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AN APPRAISAL OF THE VALUE OF RADIOLOGICAL DIAGNOSIS IN OBSTETRICS, BASED ON FIFTEEN YEARS' PERSONAL EXPERIENCE*

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THE use of x-ray diagnostic procedures in obstetrical practice is by no means a recent development, but, within the last fifteen years, there has been a relatively rapid increase in their applicability and in their accuracy. This has resulted from an intensive study by many authorities, the consequence of which has been to arouse the widespread interest of obstetricians in what has by now fulfilled earlier promises to become an important and useful aid in obstetric diagnosis.

My own interest and that of certain of my colleagues dates back about fifteen years, during which time we have gained a fairly extensive background of experience in well over a thousand cases of pelvimetry alone, in a slightly lesser number of placental visualizations, and in an uncounted but very appreciable number of other radiological obstetric examinations of a varying nature.

During this period we have felt our way cautiously and have admittedly experimented with various methods and techniques. We now believe that our experience has been sufficiently extensive to enable us to form a degree of critical judgment with regard to the usefulness of these measures that may justify an attempt to report our appraisal of their value and to assess the effect that they may have produced upon obstetrical practice in our locality.

The subject matter of this paper will be restricted to an account of our experiences and conclusions concerning x-ray pelvimetry, visualization of the placenta, mechanism and progress in labor, cephalometry, and intrauterine fetal death.

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Pelvimetry

The well-known, widely recognized, and time-tried method of Thoms, employing the centimeter grid, was utilized for a period of about seven years, following which a careful study and appraisal of all currently accepted methods were undertaken. These were of three main types, the false centimeter scale methods, the stereoscopic methods, and the proportional methods. The first of these we had already used extensively and, at that time, an objection, since overcome, was applicable, in that no reliable information was gained concerning the midpelvis. This, and our desire for greater technical simplicity, resulted in a decision in favor of the proportional method. So far as the stereoscopic procedure was concerned, it was and is obviously beset by greater technical difficulties and complexities than any other. We have therefore, employed the proportional method for the past seven years with increasing satisfaction and confidence and can report that we have encountered no fundamental or important difficulties. In our hands, we believe, it has proved to be simple, accurate, and reliable.

The actual technique which we employ is a combination of the Snow[1] method and that described by McSweeney and Moloney,[2] which is again a modification of that of Ball.[3]

No attempt need be made here to discuss the detailed technique of the method, since this is well documented in the authors' own publications. I may point out, however, that we believe the information made available concerning the floor of the midpelvis in McSweeney's and Moloney's procedure to be an important and valuable addition to the otherwise similar information provided by the Snow method.

In general terms, our experience has led us to the following broad conclusions regarding the practical applications of x-ray pelvimetry. It is desirable that this procedure be performed at term or even preferably in the early stages of labor, since it is obviously at that time that the full extent of the physiological relaxation of the pelvic girdle is evident, as is the ultimate appraisal of cephalopelvic proportions most accurate and satisfactory.

One is here often concerned with the problem of the unengaged head in a primipara at term and the point may well be emphasized at this juncture that the solution of this difficulty is frequently to be found in the taking of a lateral film in the standing position, when the unengaged head will be found to have readily accommodated itself to the inlet of the pelvis. This procedure we have found to be of distinct value, even though it does not form an actual part of the technique of pelvimetry.

1. *Shape and Dimensions of the Inlet.*—

So far as the inlet itself is concerned, we feel that the classification of its type according to its dimensions and shape is of limited value in predicting the mechanism and possible difficulties in labor, *unless* considered in conjunction with the similar characteristics of the midpelvis and outlet.

In any given instance, if we are concerned only with the factor of probable inlet dystocia, and are assured that the midpelvis and outlet will present no particular problem, our judgment concerning the ability of the head to engage in the inlet, though it has proved to be reasonably accurate, is inferior in reliability to the results of trial labor, which is to be preferred as the best criterion when the problem is confined to the inlet itself. Exception must of course be made for those relatively rare instances in which an absolute indication for section is presented, such as a true conjugate of less than 7.5 cm. in a flat pelvis or of less than 8.0 cm. in a generally contracted pelvis.

Regardless of the superiority of trial labor where the inlet alone is concerned, it is frequently the case that the midpelvis will present potential diffi-

culties in addition to the inlet and it is in these by no means rare cases that one is called upon to render judgment concerning the inlet without the aid of trial labor.

This involves more than a mere consideration of the diameters concerned and must of necessity include certain important factors which cannot be estimated beforehand, such as the strength of the powers, the moldability of the head, and the influence of the cervix in directing the head into that part of the pelvis where most room is available.

The attitude or degree of flexion of the head at the onset of labor can best be determined by x-ray examination and may have an important bearing on the outcome, regardless of all other considerations.

Apart, also, from the dimensions of the inlet, one must pay due regard to its shape, the capacity of the forepelvis and of the hindpelvis, and the possible encroachment of the promontory of the sacrum on the transverse diameter.

We agree with McSweeney and Moloney who state, "Where there is a male type of posterior pelvis, with the greatest transverse diameter of the inlet approximating the promontory by less than 3 cm. one must measure the available transverse diameter at least 3 cm. from the promontory, otherwise one may get a false concept of the roominess of the inlet."

2. *The Midpelvis.*—

We believe that the vast majority of cases of dystocia occur in the midpelvis and it is with regard to this plane that we have found x-ray pelvimetry to be of much value, particularly when the findings are given consideration in conjunction with careful appraisal of the pelvic cavity by palpation performed earlier in pregnancy.

The dimensions and characteristics in the midpelvis to which we have learned to attach the greatest importance are as follows: (a) the interspinous diameter and, particularly, its relationship to (b) the post-sagittal diameter of the floor, (c) the size and shape of the sciatic notch, especially in its relationship to the roominess or to apparent inadequacy of the forepelvis, (d) the length or depth of the anterior or foreportion of the midpelvis. This, when measured, was designated by Schuman[5] as the pubotuberous diameter, but in our experience can be adequately appraised without actual measurement, (e) the degree of convergence or straightness or divergence of the lateral pelvic walls and of the anterior and posterior bony boundaries of the pelvic cavity as they approach the outlet.

The interspinous diameter is the shortest diameter in the midpelvis. It varies from 8.5 to 10 or more cm. The vast majority are over 10 cm. and anything over 9.5 cm. may be regarded as normal. The significance of any interspinous measurement below this dimension can only be decided in conjunction with its relationship to the hindpelvis, as represented by the postsagittal diameter, and to the length or depth of the forepelvis; the degree of convergence of the lateral pelvic walls and the width of the subpubic arch. Our experience confirms the statement of McSweeney and Moloney that "if the occiput is posterior and there is a narrow subpubic arch, combined with an interspinous diameter of 9 cm. or less, at least 3 cm. is needed in the posterior sagittal diameter to permit rotation." We can further confirm that "for all practical purposes, the posterior sagittal diameter, to be adequate for rotation, should measure at least one-third of the interspinous diameter."

The interrelationship of the factors just enumerated frequently determines the mechanism of any given labor. For example, a long forepelvis and narrow subpubic arch with, perhaps, a short interspinous diameter, in association with a generous sciatic notch and a correspondingly long postsagittal diameter

at the level of the spines will indicate that descent will best be accomplished with the occiput posterior. This may be regarded as the mechanism of choice in such a pelvis and any attempt to alter it would be inadvisable.

It is obvious that in the operative management of midpelvic dystocias such knowledge as can be gained by this means must be regarded as virtually essential information, which is a prerequisite to the intelligent conduct of the operative delivery. It follows also that such knowledge can be invaluable in the delivery of breech, as well as vertex presentations.

3. *The Pelvic Outlet.*—

Although the posterior sagittal and intertuberous diameters of the outlet are routinely measured by x-ray examination and the information obtained thereby is undoubtedly reliable and useful, it is my own tendency to base final judgment concerning this plane upon the results of palpation and external outlet measurements, since, after all, this is the one plane of the pelvis which can be satisfactorily and accurately appraised without the aid of x-ray.

Having found no consistent relationship between external pelvimetry and x-ray pelvimetry over a period of seven years, it has since become my practice to perform x-ray pelvimetry at term in all primigravidas and in any multigravida with a history of dystocia. The films, not merely the report thereon, are available for examination and study during labor.

Further film studies, without the inclusion of pelvimetry, may be made during the course of labor, as indicated. These are frequently of great assistance, in determining position, station, and attitude with accuracy. This practice has materially diminished the incidence of vaginal examinations and it is not unlikely that the conclusions drawn therefrom may well have been more consistently accurate than those derived in the past from vaginal palpation.

An interesting observation which has presented itself not infrequently in our experience with x-ray pelvimetry concerns the problem of the full bladder. It seems perhaps superfluous to refer to this simple and inexcusable cause of dystocia before this audience but it may be of interest to mention that, not infrequently, patients in labor with arrested descent are sent for x-ray pelvimetry with the tentative diagnosis of cephalopelvic disproportion and the possibility of cesarean section under serious consideration and are found to have a full bladder and no disproportion. The recommendation of the radiologist concerning catheterization has been so often followed by rapid descent and delivery that one is irresistibly prompted to suggest that this is at least a very expensive manner in which to solve a dystocia problem.

A tendency has been observed to accept, without careful judgment as to its real significance, the presence of a contracted diameter or diameters as a contraindication to vaginal delivery. By this I mean that I believe that x-ray pelvimetry has, in itself, been responsible for an increase in the cesarean section rate. This should not be regarded as a justifiable criticism of x-ray pelvimetry, nor does it detract from its importance or usefulness. It does, however, serve to emphasize that its employment demands experience and judicious application and that it must be regarded only as an important adjunct to facilitate the more accurate application of obstetric knowledge, experience, and judgment. It cannot be too loudly proclaimed that, in no way whatever, can x-ray pelvimetry substitute for these qualities.

The radiologist who presumes to prognosticate, solely on the basis of the pelvic measurements, however accurate they may be, is assuming an unwise responsibility if he disregards his probable ignorance of the mechanism of labor, and of the many other factors with an important bearing on the outcome.

Equally misguided is the clinician who is prepared to form conclusive judgment on the basis of mensuration alone. Without experience in the interpretation of obstetric x-ray films, a sound knowledge of the mechanism of both normal and abnormal labor, and a proper appreciation of pelvic architecture, his judgment is likely to be most fallacious.

4. *Placental Visualization.*—

From the time that Vaughan, Weaver, and Adamson[6] described the method of placental visualization by the plastic filter technique we have employed this procedure in every patient who submits to x-ray pelvimetry and in any patient in whom vaginal bleeding in the last trimeter may have suggested the possibility of an abnormally situated placenta.

The results, we feel, have fully justified this policy and in several instances we have been able to establish the diagnosis of placenta previa before bleeding has occurred.

As technical experience increased, more accurate interpretation of the films was facilitated and it is now a rare event to encounter any doubt as to the location of the placental site. The normally situated placenta can be delineated with practically 100 per cent accuracy. Occasionally it may be difficult to decide as to whether the lower border of a low-lying placenta may or may not be encroaching upon the lower uterine segment, but, as our experience has increased, we find this doubt occurring with diminishing frequency.

In no instance where section has been performed after the x-ray diagnosis of placenta previa, have the operative findings failed to confirm the accuracy of the diagnosis. Conversely, in no instance where the placenta has been demonstrated and declared to be normally situated, have subsequent developments contradicted this evidence.

In a relatively few cases vaginal examination has been regarded as necessary to confirm inconclusive x-ray findings but it is nevertheless the case that the incidence of vaginal examinations in the diagnosis of placenta previa has been very materially reduced since x-ray diagnosis was introduced. It is hardly necessary to comment on the value of this in minimizing both morbidity and blood loss.

Very rarely has it been found useful to obtain confirmatory evidence in doubtful cases by the injection of air or contrast medium into the bladder or rectum. When this procedure has been employed it appears that satisfactory results have been obtained only in vertex presentations with the exposure taken with the patient in the standing position.

We have found that the soft tissue technique may be rendered uncertain and inconclusive by the presence of hydramnios.

Experience has shown an appreciable incidence of films in which the findings are not as satisfactory or conclusive as might be desired and we have found that, since these exposures are taken in lateral view, this difficulty can usually be overcome by another film taken with the patient lying on the side opposite to that in which the first unsatisfactory exposure was made. Accordingly, each placental film is examined before the patient is released and a second film or third made if necessary.

5. *Intrauterine Fetal Death.*—

Apart from the classical and well-known radiological signs of fetal death, such as Spalding's sign, we have observed in two cases another sign which we believe to be of interest and value. I refer to the presence of radiolucent collections of gas in the major vessels of the fetal circulatory tree. This observation was reported by Roberts[7] in 1944. In both instances fetal death was suspected by reason of cessation of fetal movement and failure to detect the

presence of fetal heart tones. In neither case was any other evidence of death detectable by x-ray examination and the diagnosis, subsequently confirmed, was made on the presence of this sign alone. We feel that this evidence must be unusual, but that it is nevertheless reliable, when present, and should be borne in mind.

6. *Cephalometry.*—

Estimation of the size, circumference, and diameters of the fetal head, if reasonably and consistently reliable, would be of the greatest value in predicting cephalopelvic proportions. We recognize that this is attempted by various methods and with varying degrees of success. Suffice it to say here, however, that in our hands it has not proved to be consistently reliable or of real practical value. In fact, we have found it to be often misleading. This observation may perhaps be consequent upon our own limitations and deficiencies but it is at least our present opinion, that, most certainly in breech presentation, almost invariably in the unengaged vertex presentation, and generally in the engaged vertex, it is not possible to perform cephalometry with the dependable degree of accuracy which would justify a conclusive opinion regarding cephalopelvic proportions.

Conclusions

1. We believe that x-ray pelvimetry, judiciously employed, is a reliable and important adjunct to obstetrical practice and that it may be usefully employed in rendering obstetric judgment more accurate. We wish to refute any suggestion or implication that it can be substituted in whole or in part for sound obstetrical knowledge.

2. Placental visualization by the soft tissue technique we have found to have a highly practical degree of accuracy and, in our hands, it has not proved to be misleading, even though it has not been infallible. We are confident that it has been responsible for the conservation of blood and the prevention of at least potential infection in many instances. It has perhaps saved the lives of certain mothers and babies, the number of which can only be conjectured. It has repeatedly relieved the obstetrician of unnecessary anxiety and doubt.

3. A sign of intrauterine fetal death, which is believed to be reliable in the absence of other characteristic signs, has been described.

4. The usefulness of x-ray examinations during the course of labor, to determine position, station, and attitude and in minimizing vaginal examinations, has been emphasized.

5. Our experience in attempted x-ray cephalometry is reported as having proved disappointing, so far as practical accuracy is concerned.

6. We regard the ready availability of x-ray examination as an important part of our obstetrical diagnostic armamentarium and as an essential adjunct to our labor room facilities. We have in the past, and will in the future continue to employ it as such.

References

1. Snow, William: Clinical Roentgenology of Pregnancy, Springfield, Ill., 1942, Charles C Thomas.
2. McSweeney, D. J., and Moloney, A. M.: New England J. Med. **223**: 1043-1049, 1940.
3. Ball, R. P.: Am. J. Obst. & Gynec. **32**: 249-257, 1936.

4. Ball, R. P.: Radiology **31**: 188-197, 1938.
5. Schuman, W.: Am. J. Obst. & Gynec. **28**: 497-500, 1934.
6. Vaughan, C. E., Weaver, R. T., and Adamson, D. L.: Canad. M. A. J. **46**: 314-320, 1942.
7. Roberts, J. B.: Am. J. Roentgenol. **51**: 631-634, 1944.

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Discussion

DR. W. R. FOOTE, Montreal, Quebec.—Dr. Nash's personal experience with x-ray diagnosis in obstetrics parallels that of many obstetrical clinics. Our clinic has been partial to the Thoms method after carefully comparing it with that used by Dr. Nash; others prefer some other modification—which suggests that there are many methods of x-ray mensuration equally accurate with definite usefulness and equally definite limitations.

Certainly, the shape of the pelvis, the pelvic contour in the three planes, is more important than the measurement of fractions of centimeters. While the superior plane of the pelvis is readily judged for cephalopelvic disproportion by clinical and x-ray examination, the midpelvis still offers a great problem in certain cases. Here we are too familiar with that posterior position, inertia, poor cervical dilatation, impaction in the posterior with insufficient diameters for rotation. A lateral erect roentgenogram is of great assistance in estimating possible cephalopelvic disproportion in the midplane but sometimes I find the x-ray and my judgment sadly deficient. I stress one point made by Dr. Nash, with which some will not agree. All impacted posteriors should not be rotated or at least attempted to be rotated anteriorly. Some should be deliberately delivered face to pubes; that is, the occiput posterior in the pelvis with the narrow subpubic arch, a short intraspinous diameter, and a generous sacrosciatic notch or posterior sagittal diameter.

As regards the outlet, I sincerely believe that you cannot measure it accurately by x-ray—the variation in the pelvic inclination, the awkwardness of posturing the patient will often throw a false image of the subpubic arch. Why bother when the inferior strait is the most accessible of all the pelvic planes for clinical estimation? Why do we still persist in emphasizing the use of the caliper when we should be concentrating on the internal examination, on the slope of the side walls, the ischial spines, the curve of the sacrum, etc.?

Measurement of the fetal head in utero by volume or diameter is inaccurate and often leads to false conclusions by the roentgenologist as to the presence of cephalopelvic disproportion. The x-ray film will give the pelvic contours but the obstetrician by judgment and experience must decide whether or not the baby will pass through the pelvis. Even when the roentgenologist dictates on his report that cephalopelvic disproportion is present the clinician must make the final decision and if the latter accepts the x-ray reports at face value he will do many unnecessary cesarean sections.

Placental visualization in our clinic still leaves much to be desired. I cannot help feeling that too much reliance should not be placed on the x-ray diagnosis. Where the placenta is demonstrated to be out of the pelvis—unnecessary examinations will be avoided but there must be many cases where the placenta is demonstrated to be low where a vaginal examination will show a marginal placenta easily controlled by rupture of the membranes and thus a needless cesarean section will be omitted.

DR. N. W. PHILPOTT.—I would like to suggest that those obstetricians who are interested in pelvoradiography should take periodic checks on the condition of the patient through the course of hard labor. I am sure it will be found by them that in many instances there will be gradual regression rather than progress in descent of the presenting part.

DR. NASH (Closing).—Dr. Foote has emphasized the value of experience and no one in my opinion is more dangerous than he who will—without real knowledge—draw quick conclusions from x-ray films. Experience increases the tendency to disregard the actual measurements. If I had to choose between an x-ray report and a personal viewing of the films, I would take the films and disregard the report.

PERITONEAL IRRIGATION IN THE TREATMENT OF ACUTE RENAL FAILURE*

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THE concept that the peritoneum can be used as a dialyzing membrane for the removal of metabolic products is not new in animal experimentation. Abel[1] and his associates suggested this method as a treatment for anuria and uremia in 1914. Seligman, Frank, and Fine,[2] working on nephrectomized dogs, were able to maintain about 40 to 75 per cent of normal kidney function in terms of urea clearance and correcting acidosis. They were the first to use this method successfully on human beings. For the peritoneal irrigation, they used many solutions, saline, glucose, glucose-saline, Ringer's solution, and finally decided on a modified Tyrode solution to which is added heparin, penicillin, sulfadiazine and, added by others and ourselves, streptomycin, as the one giving the best results.

These investigators tried irrigation of intestinal loops but found it unsatisfactory as about 200 inches of bowel would be necessary to simulate the results of peritoneal irrigation. They tried the pleural cavity as well.

It was soon discovered that the maintenance of a proper electrolyte balance in the extracellular fluid was more important than the reduction of the azotemia. Water can be removed too rapidly from the plasma. The same applies to glucose and maybe to other substances. The lives of the uremic nephrectomized dogs were prolonged three to ten days by peritoneal irrigation. They did not die of uremia.

To understand better the mechanism of this procedure, a review of some of the newer concepts of the biochemistry and pathology involved is presented. Marriott[3] has published an excellent review on water and salt depletion. Gamble[4] has shown that the composition of plasma and tissue fluid is the same except for the protein content, and that two-thirds of the body sodium chloride is contained in them (Fig. 1). Both are extracellular fluids and it is probable that hundreds of liters a day exchange between the capillaries and the interstitial tissue. The balance in the plasma volume is maintained by hydrostatic pressure, plasma protein osmotic pressure, and tissue fluid pressure.

Intracellular fluid has very little sodium and chlorine except for a small amount in the red blood cells. The osmotic isotonicity of the tissue fluid is an important factor in the proper functioning of the cells. The chlorine anions can be replaced by bicarbonate ions, but there is no substitute for the sodium kations in the extracellular division (Fig. 1). In simple water lack the extracellular fluid loses water and as a result intracellular water decreases, so eventually it is chiefly a loss of cellular water. In salt depletion the extracellular fluid is hypotonic and the kidneys excrete water to maintain balance. Urinary output to a certain extent depends upon its concentration but the minimum possible to get rid of the solids is about 500 c.c. "urine obligatoire."

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The body economizes salt better than it does water. Some persons become salt logged rather than water logged, requiring water to get rid of the edema. Sodium and chlorine are the chief constituents of extracellular fluid. They maintain the acid-base balance. Even with a liberal supply of water they can be lost, e.g., in vomiting, diarrhea, fistulas, etc. In vomiting there is a relatively greater chlorine depletion with a tendency to alkalosis; in diarrhea, there is a relatively greater sodium loss with a tendency to acidosis. In heat exhaustion, even when drinking much water, salt is depleted. We find that in these patients the plasma sodium and chlorine drop, the blood urea rises, and the urine urea drops. Hemoconcentration takes place and the blood viscosity rises. The last two lead to renal anoxia, which is followed by anuria and then coma.

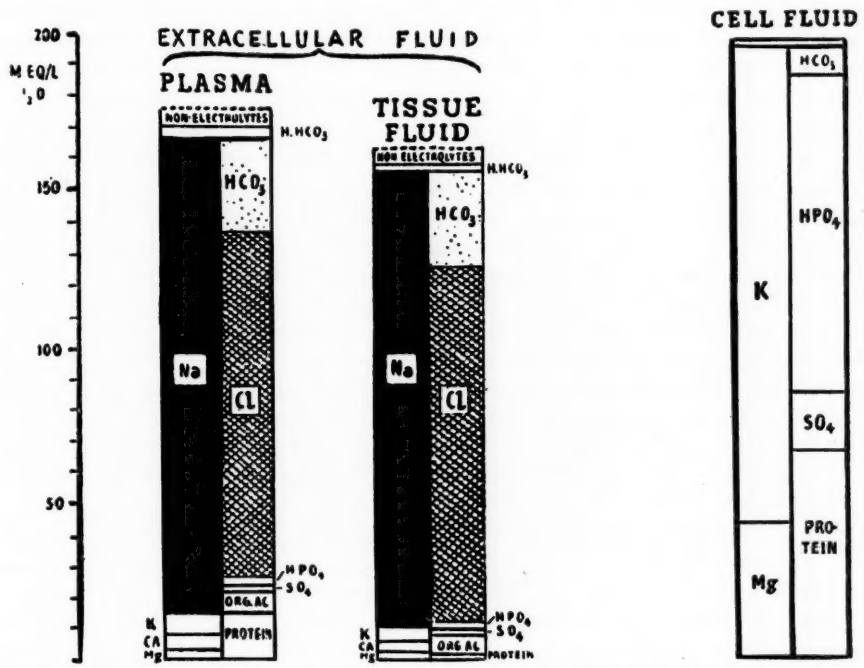

Fig. 1.—Composition of plasma and tissue fluid extracellular and that of intracellular fluid scale in milliequivalents per liter of water. (By courtesy of Dr. J. L. Gamble.)

Lucke[5] has demonstrated recently that patients dying of acute renal failure due to different causes, such as crush syndrome, abruptio placentae, toxemias of pregnancy, transfusion reaction, burn, and heat stroke, etc., all exhibit the same kidney lesion. There is degeneration and necrosis in the distal segments of the tubules. He calls this picture, "lower nephron nephrosis." In all the cases there was destruction of tissue or blood. Shock appeared early and was followed by renal insufficiency. The shock came on immediately or within a few hours and was easily treated. The urinary output remained low after recovery from the shock. The urinary output was less than 500 c.c. The specific gravity of the urine was low. Benzedrine reaction in the urine was positive, due to a heme pigment. Azotemia was always present, the nonprotein nitrogen was over 150 mg. per cent. The potassium and phosphorus were raised and the alkali reserve lowered. The blood pressure came down with the shock, rose later, and stayed up. Edema was not always present. Uremia developed and the course was brief, three to ten days. Ninety-five per cent of the cases were fatal before the eighth day.

Pathological Anatomy

The kidney lesion is the same in all cases of acute renal failure. The kidney is swollen, weighs 400 to 600 Gm., is flaccid, the capsule strips easily, the outer surface is pale, and the cut surfaces ooze and are slightly bloody. The cortex is widened, bulges, and is pale in contrast to the dark medulla. The striations are accentuated. The gross appearance is not pathognomonic. Microscopically, one finds degeneration or necrosis in selective focal portions of the lower segments of the nephrons, i.e., in the thick tubules of Henle and the distal convoluted tubules. There are edema and cellular reaction around the damaged portions of the tubules. Thrombosis of the adjacent veins is common. Casts of a heme compound are found in the lower segments and collecting tubules. There is very little change in the upper parts of the nephrons. The glomeruli are relatively normal. The proximal segment may show some cloudy swelling. The lower segment is selectively involved. The tubules degenerate early and then necrose focally in small areas sometimes rupturing the lumen. After the fifth day the necrotic portions disintegrate and disappear. Regeneration begins after the third or fourth day, new cells developing. In about ten days most damaged areas are completely relined.

The heme casts found are of two varieties. One is hemoglobin, whose molecule under normal circumstances is too large to pass the pores of the glomerular capillaries (molecular weight about 70,000). In this condition some do pass into the urine probably due to increased glomerular permeability. If sufficient hemoglobin is injected intravenously hemoglobinuria results and is probably excreted through the kidney by this mechanism. The other cast is myohemoglobin with a molecular weight of about 17,500. This molecule passes readily through the glomerular capillaries. Some of it is resorbed. Most of it goes to the lower segment where some is precipitated as acid hematin due to the pH here being below 6. This accounts for the wide use of alkalies in muscle trauma and intravenous hemolysis to prevent this acidity and precipitation of hematin.

After injury the total circulatory volume may be reduced to one-half, but the flow through the kidneys may be decreased to one-tenth, or one-twentieth. Hence, the oliguria or anuria. The main factor in injury to the nephrons is renal anoxia. This ischemia and subsequent anoxia are basically important. Haldane stated, "Anoxia not only stops the machinery but also wrecks the machine."

Peritoneal irrigation was used by us on a case by the method described by Fine, Frank, and Seligman[6] with some modifications. A 25-year-old white woman was admitted to the Jewish General Hospital of Montreal on Nov. 28, 1946, with a diagnosis of thromboasthenic purpura complicating pregnancy. Her complaints were bleeding gums for two months, purpuric spots on all extremities for one week, and absence of fetal movements for two months.

On her first visit to her physician in September, 1946, she complained of edema of her face, hands, and legs. She was about seven months pregnant. Her blood pressure was normal and urinalysis was reported negative. The fetal heart could not be heard. There were no fetal movements and the fetus was presumed to be dead. With bed rest and a salt-free diet the edema cleared up in about ten days. She was followed carefully for about two months and, when she was close to term, she noticed that the gums were bleeding profusely and that purpuric spots appeared on her body. A hemogram done at this time showed 4,100,000 red blood cells per cubic millimeter; hemoglobin 80 per cent, numerous platelets which did not disintegrate normally, bleeding time seven and one-half minutes, clotting time over four and one-half hours, prothrombin time 42 seconds (normal 15 to 19 seconds); Rumpel-Leede test negative; blood grouping A, Rh negative.

She was then admitted to the Jewish General Hospital. She had had three previous deliveries elsewhere. The first, in 1940, was a long labor with postpartum bleeding, and she received a transfusion of her husband's blood. After a stormy convalescence she went home with a living child. Her second labor in 1942 was spontaneous but terminated in a dead fetus. Her third labor in 1943 was spontaneous at term and resulted in a living child.

On admission she was transfused with 500 c.c. of citrated whole blood. She had a severe chill immediately afterwards, her temperature rising to 101.3° F. Although the donor's blood was first reported Rh negative, on rechecking it was found to be Rh positive. She went into labor and eleven hours after admission delivered spontaneously a macerated fetus of about seven months. Catheterization at delivery yielded only 2 ounces of bloody urine. In spite of a well-contracted fundus, and oxytocics both intramuscularly and intravenously, she had a severe postpartum hemorrhage and the uterus had to be packed. She was given plasma, blood, glucose, vitamins C and K, calcium gluconate intravenously and in twenty-four hours the bleeding was controlled. A hemogram taken thirty-six hours after admission was normal except for a slight anemia.

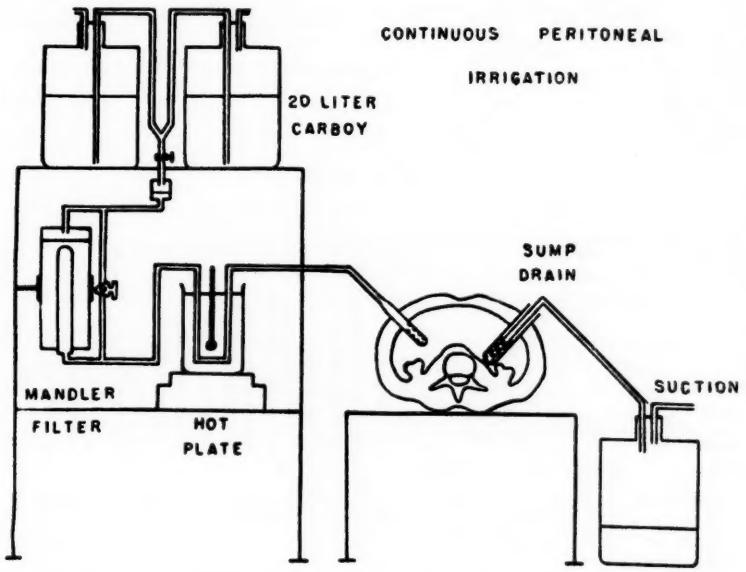

Fig. 2.—Diagrammatic representation of the circuit for continuous peritoneal irrigation. (By courtesy of Dr. J. Fine.)

Oliguria continued, urine was bloody, with many granular casts and for three days, in spite of diaphoresis, hot poultices to loins, intravenous glucose, ureteral catheterization, and lavage of kidney pelves, the oliguria became more marked and azotemia progressed.

At this point peritoneal irrigation was instituted and carried on for ten days (Fig. 2). The solution was run in by gravity from large flasks through a Y-tube into a drip bulb, through a Berkefeld filter, into a U-tube over a water bath at 42° C., and finally into the peritoneal cavity. The filter candle should permit a flow of 40 to 60 c.c. per minute. Sump drains were inserted under local anesthesia into each flank. The inlet tube points towards the mesentry, the outlet into the pouch of Douglas. The outlet tube is connected to a large graduated jar to which is attached a suction pump. Maximum blood clearance was found when the rate of flow was about 60 c.c. per minute. At the same time we carried on with supportive therapy such as blood transfusions, intravenous glucose, vitamins and amino acids. The composition of the irrigating fluid was varied according to the demands of the patient's electrolyte balance.

About the tenth day the tubes had to be manipulated as they were becoming blocked with fibrinous deposits in spite of the heparin. The tubes were removed on the eleventh day. A few hours before the tubes were removed the patient had a generalized convulsive seizure. In spite of calcium gluconate, 50 per cent glucose intravenously, and Luminal Sodium, the convulsions recurred irregularly. The idea was entertained that these seizures were caused by an electrolyte shift between extra- and intracellular fluids due to a loss of extracellular sodium in the irrigating fluid. Normal saline was given intravenously with dramatic results. The seizures stopped immediately. Later this therapy was discontinued for thirty-six hours, and the seizures recurred. Once more they were controlled promptly with saline. This treatment was given daily thereafter. By this time, fortunately, sufficient renal function had returned to enable adequate clearance of nitrogenous products from the blood, in spite of the cessation of the irrigation and the convulsions.

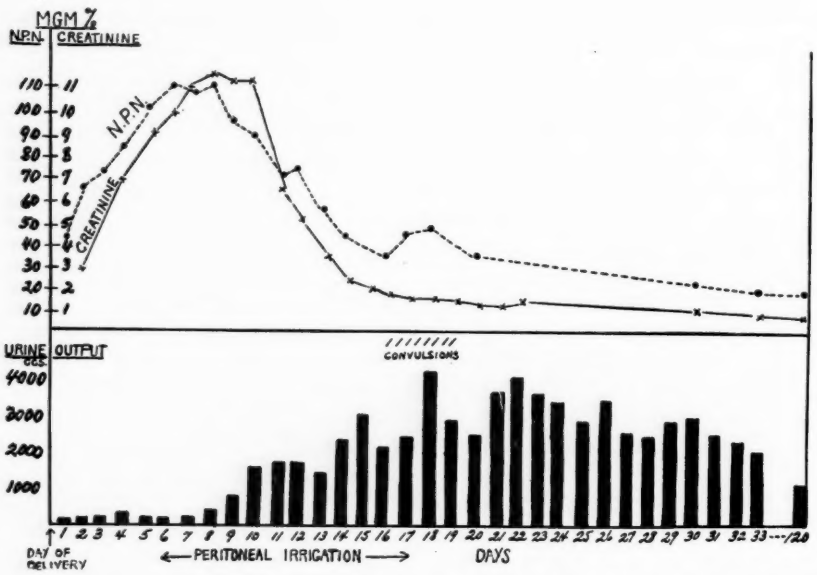

Fig. 3.—Chart showing reduction in azotemia and increase in urinary output following the institution of peritoneal irrigation.

The urinary output increased very rapidly after the institution of the peritoneal irrigation, doubling within the first twenty-four hours. Abnormal findings in the urine disappeared rapidly but the specific gravity remained low. Thirty-three days after admission the patient was discharged. Blood chemistry findings were within normal limits, urinary output was about 2,400 c.c. in twenty-four hours with a specific gravity of 1.010 to 1.013. Four months later the urinary findings were normal with a specific gravity up to 1.033. The dose of the salt tablets which she had been taking was decreased and stopped about a month before.

On June 10, 1947, a laparotomy for a large ovarian cyst was done during which time the peritoneal cavity was examined and found to be completely free of adhesions.

Summary

Lucke has applied the term "lower nephron nephrosis" to the kidney lesions in acute renal failure due to various causes, because it is mainly the lower segment of the nephron which is involved. The lesions vary from focal degeneration to necrosis and disintegration of the epithelium in the tubules in Henle's loop and the distal convoluted tubules. In renal shutdown after a

varying period of time diuresis starts and polyuria develops, which is mostly an unconcentrated filtrate. Some time must elapse for regeneration of the tubular epithelium before adequate concentration can take place. In the case reported diuresis and blood clearance were established soon after the peritoneal irrigation was started. However, it took several months before the urine concentrated to 1.033.

Peritoneal irrigation in the treatment of renal failure can only be applied successfully when the pathologic changes are reversible. Where the renal lesion is permanent one can only prolong life for a short while, but where the damage is such that sufficient functioning tissue will regenerate if given time, it is possible to control the azotemia temporarily so that adequate kidney function can be established. The use of this method in the treatment of a patient with acute renal failure is reported; also demonstration of the control of the generalized convulsions with saline. It took almost four months for the urinary findings to become normal.

The patient referred to in the case report cited in this paper was referred to the author by Dr. Max Wiseman.

The peritoneal irrigation was carried out with the cooperation of Drs. Morton Korenberg and Joseph Portnuff.

References

1. Abel, J. J., Rowntree, W. G., and Turner, B. B.: J. Pharmacol. & Exper. Therap. **5**: 275, 1914.
2. Seligman, A. M., Frank, H. A., and Fine, Jacob: J. Clin. Investigation **25**: 211-219, 1946.
3. Marriott, H. L.: Brit. M. J. **1**: 245-250; Feb. 15, 1947; **1**: 285-290, Mar. 8, 1947; **1**: 328-332, Mar. 15, 1947.
4. Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, Cambridge, Mass., 1942, Howard University Press.
5. Lucke, Baldwin: Mil. Surg. **99**: 371-396, 1946.
6. Fine, Jacob, Frank, H. A., and Seligman, A. M.: Ann. Surg. **124**: 857-878, 1946.
7. Frank, Howard A., Seligman, Arnold M., and Fine, Jacob: J. A. M. A. **130**: 703-705, 1946.
8. Kolff, W. J., and Berk, H. T. J.: Acta med. Scandinav. **117**: 121-134, 1944.
9. Rhoads, J. E.: Am. J. M. Sc. **196**: 642-647, 1938.
10. Goodyear, W. E., and Beard, D. E.: J. A. M. A. **133**: 1208-1210, 1947.
11. Odel, Howard M., and Ferris, Deward O.: Proc. Staff Meet. Mayo Clin. **22**: 305-314, 1947.
12. Muirhead, E. E., Small, A. B., Haley, A. E., and Hill, J. M.: J. Lab. & Clin. Med. **32**: 988-1002, 1947.

Discussion

DR. J. S. L. BROWNE, Montreal, Quebec.—Dr. Strean has emphasized the importance of anoxia of the kidney in the production of renal shutdown. Van Slyke and his collaborators and Cournand and Richards and their collaborators have shown both for dogs and for human beings that the renal flow is reduced after injury even before much change occurs in the general arterial pressure. The renal ischemia seems to be a compensatory mechanism under these conditions and there appears in the blood an increased amount of the renal pressor substances. In addition to a period of prolonged low blood pressure as a factor in the production of this syndrome, the existence of anemia either preceding the trauma or operation or occurring as a result of it is a factor in the production of tissue anoxia.

In estimating the efficacy of peritoneal transfusion as a therapeutic measure it is important to realize that there are all degrees of damage to the kidney depending on the length of time over which anoxia persists. Van Slyke has shown that if anoxia is produced in a dog's kidney for a certain time renal shutdown occurs, the nonprotein nitrogen

rises, then urinary flow is spontaneously re-established, and recovery occurs. After more prolonged anoxia permanent shutdown follows and death occurs. The type of case in which peritoneal lavage will be lifesaving is presumably the one in which recovery of the kidney is possible but the metabolic consequences of failure of renal function are so great as to destroy the organism before this recovery can take place. It is very difficult to judge in any particular patient whether spontaneous recovery is going to take place and therefore to judge the therapeutic effect of the lavage.

In this connection I may quote briefly two cases.

One was a patient of Dr. P. J. Kearns, a woman, aged 29 years, who had a spontaneous miscarriage at about seven weeks with considerable bleeding. She was brought into the hospital and a curettage performed. She had a prolonged period of low blood pressure and was given plasma and whole blood. Only 50 c.c. of urine were obtained by catheterization the first day, the second day about 400 c.c., some being lost by involuntary micturition, the next day 1,220 c.c., specific gravity of 1.010, and the following day 3,820 c.c. The nonprotein nitrogen rose to 115 mg. per cent three days after admission and the creatinine to 6.6 mg. per cent. The bilirubin rose to 11.1 mg. per cent three days after admission and the patient was deeply jaundiced. The blood chlorides were low and the cephalin-cholesterol flocculation test was 3 to 4 plus. The values gradually fell, the nonprotein nitrogen to normal on the tenth day, the bilirubin reached normal on the thirteenth day after admission, and the patient recovered with no residual renal damage.

This is a case then of transient renal shutdown. The patient was given plasma and 500 c.c. of whole blood on the evening of the curettage. No chill or reaction followed immediately, but later the patient complained of hot and cold sensations. This brings up the point that while such renal shutdown and jaundice do follow incompatible transfusions it should be remembered that it is precisely the conditions for which whole blood is given, that is a period of low blood pressure and anemia, which lead to renal shutdown and liver damage from anoxia and the occurrence of such a state under these conditions should not be immediately attributed to a transfusion reaction in the absence of evidence of incompatibility.

Another case was well studied and treated by Dr. J. Harkness of the Lachine General Hospital. This patient had an abrupt retroplacental hemorrhage into the substance of the uterus at the eighth month of pregnancy. She collapsed, with a low blood pressure and anemia. She was operated upon after transfusion and the uterus removed. Renal shutdown followed with gradually rising nonprotein nitrogen and finally with convulsions nine days later. Peritoneal lavage was instituted and carried on for a total of thirty-five days. The nonprotein nitrogen was successfully reduced to 66 mg. per cent. About a week later marked muscular hyperirritability and twitchings developed. The Chvostek sign was negative but the blood calcium was found to be 5.8 mg. per cent. Glucose saline and thiamine had failed to control the twitchings, but they promptly ceased with intravenous calcium gluconate. The peritoneal lavage fluid going into the abdomen was found to contain 2.75 mg. per cent calcium and coming out 3.15 mg. per cent; this may seem a small difference, but as 40 liters were being used per day, about 160 mg. calcium were being lost per day with no intake. It should be remembered that this was diffusible calcium and that ordinarily when the blood calcium falls below 7.0 mg. per cent none appears in the urine. In this case calcium continued to be lost in the peritoneal lavage with a blood calcium considerably below this.

As Dr. Strean has mentioned, any substance, electrolyte, vitamin, etc., which is freely diffusible and the concentration of which is lower in the peritoneal lavage fluid than in the blood will be removed from the body by this procedure and if the lavage is carried out over a prolonged period the body will be depleted of these constituents. This patient's urine volume never rose to more than 800 to 1,000 c.c. per day, with a specific gravity of 1.010 to 1.012, and she died six weeks after the original hemorrhage. In this case, then, life was certainly prolonged by the lavage, but the kidneys did not recover. Incidentally, she developed marked bronzing of the skin in the last week of life and at autopsy the adrenals showed calcification and thrombosis. At autopsy there was definite loculated infection of the peritoneum, though penicillin and sulfonamides had been added to the fluid.

Pearson of the Mayo Clinic mentions the presence of hypocalcemia on the third day of peritoneal lavage in a case of carbon tetrachloride poisoning. It should be noted that renal failure and uremia with its consequent rise of blood phosphorus tend to lower the level of blood calcium and patients may develop tetany from this without peritoneal lavage. Presumably the loss of calcium by peritoneal lavage might be sufficient to cause overt tetany in cases of renal failure.

The nutritional state of the patient before the hemorrhage or trauma is in my opinion important with regard to the likelihood of collapse and renal and liver damage. Persons depleted of protein are more likely to show such damage.

Also, it may be mentioned that the rate of accumulation of nitrogenous end products in renal shutdown is dependent not only on the rate of elimination by the impaired kidney or by other channels but also on the rate of protein catabolism. The use of a high-carbohydrate, low-protein diet or the administration of adequate carbohydrate intake parenterally is important. Testosterone was used in a case of carbon tetrachloride poisoning to reduce the rate of protein breakdown. However, it is found that in persons without renal damage the rise in urinary nitrogen which occurs after acute injury or infection cannot be prevented by a high carbohydrate intake. In the presence of renal shutdown the existence of such an acute protein catabolism will cause the nonprotein nitrogen to rise more rapidly than if the kidneys had shut down without acute injury or infection.

In connection with the attempt to prevent and slow the accumulation of nitrogenous end products it should be remembered that we are ignorant of the nature of the toxic substances in uremia and as to whether their accumulation parallels that of the known nitrogenous end products.

Thus the technique of peritoneal lavage may be of value in tiding over a patient whose kidneys will ultimately recover, but who will die from the retention of unknown substances without this temporary aid. It is difficult to judge whether any particular patient will spontaneously recover without peritoneal lavage even if blood nitrogen levels reach high values, and the technique itself will deplete the body of any diffusible constituent whose concentration in the lavage fluid is lower than its concentration in the blood.

DR. ARTHUR PURDY, Toronto, Ontario.—I would like to report a case of this kind at the Toronto Western Hospital in which we used this method of treating the uremia. The case was one of septic abortion treated with sulfathiazole orally for the first tweny-four hours but as the patient was then unable to take it by mouth she was given the drug intravenously (patient had been given sulfathiazole at an earlier time to treat a common cold). Oliguria developed on the third day and complete anuria on the fourth day after starting the drug. A cystoscopic examination was done and all methods such as intravenous glucose and short-wave therapy over the kidneys to promote diuresis were tried with no effect. The method described by Dr. Strean was then used to clear her blood stream of nitrogenous end products and six hours after starting irrigation the blood nonprotein nitrogen dropped from 147 mg. per cent to 130 mg. per cent. The nonprotein nitrogen of the outcoming irrigation fluid was the same as that of the blood. Within five days the patient's kidneys were functioning again and she left the hospital within a month with a nonprotein nitrogen of 39 mg. per cent.

DR. MAUGHAN.—I should like to ask Dr. Strean on what types of cases with anuria he has used this method.

DR. STREAN (Closing).—This method of artificial diuresis has been used in cases of carcinoma causing constriction of the ureters but at our hospital we have used it only in treating sulfonamide poisoning and transfusion reactions with anuria. The irrigation solution as it is returned looks just like urine. I feel that the method should be used in cases where one has nothing to lose and everything to gain. When the patient has permanent kidney damage peritoneal irrigation just prolongs the agony with the unfavorable outcome being delayed but not averted.

RUPTURE OF THE UTERUS*

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RUPTURE of the uterus is a comparatively rare accident encountered only a few times in the life of each individual obstetrician. It is always dramatic and, too frequently, tragic in its outcome. When encountered it calls for skill in diagnosis, good judgment, and energetic treatment if bad results are to be avoided. Because of its rarity, perhaps, too little thought has been given to this accident and its implications. With this in mind, the cases occurring in the obstetric wards of the Toronto General Hospital during the twenty-year period, 1927 through 1946, have been reviewed.

Statistically, such a study is unimportant as the number is small, there being only fifteen cases of rupture of the uterus in 17,455 deliveries or one in 1,163, a comparable gross incidence with other figures published. Much more important are the lessons to be learned from the clinical aspects, for this has thrown some doubt on what, until recently, have been considered well-accepted practices in obstetrics. An attempt will, therefore, be made to stress the shortcomings of our treatment and to suggest what is for us a slightly changed approach to certain obstetrical problems.

The cases are divided as usual into three classes: (1) spontaneous, (2) manipulative or traumatic, and (3) rupture of the scar of a previous cesarean section. Their distribution is shown in Table I, and they will be considered in this order.

Table I. Rupture of the Uterus, 1927-1946

Total deliveries	17,455
Number of ruptured uteri	15
Gross incidence	1:1,163
Division of cases:	
(a) Spontaneous	1
(b) Manipulative	9
(c) Rupture of the scar	5

Spontaneous Rupture.—If one is to consider in this group only those cases in which there was absolutely no interference with labor, there actually were none in our series; however, it seemed reasonable to include under this heading the one case where the use of Pituitrin was the only added factor. Here our figures are at variance with others published. Delfs and Eastman, for instance, report 17 spontaneous ruptures out of 55 cases occurring at Johns Hopkins from 1900 to 1944. Why there should be this difference it is impossible to say, unless it be that they occurred in the earlier years of their report, before the common use of cesarean section.

Our patient was thirty years old, had had five previous spontaneous deliveries, and her largest baby weighed 11½ pounds. She was given castor oil and quinine as a medical induction. Later in the morning her membranes were ruptured and she started in labor,

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having good hard pains but making no progress, so ½ c.c. of Pituitrin was administered after which her pains became extremely severe. At the end of another three hours, morphine, grain ¼, was given with little relief. Four hours later she was admitted to hospital in collapse, showing the typical signs of rupture of the uterus. She was transfused and the abdomen opened. The child was a moderate hydrocephalic. Hysterectomy was performed, but four days later the patient died of peritonitis.

This case illustrates what are perhaps the two most common mistakes resulting in this type of rupture, first, the abuse of Pituitrin, and, second, the failure to recognize obstructed labor in a multipara.

Pituitrin in the hands of the wise is a useful and important drug. Every obstetrician knows its value. Its abuses are well recognized and well publicized, and yet it is doubtful if we always use it as we should. Furthermore, we bear the responsibility of impressing upon the profession at large its dangers and limitations. We must constantly keep before them the very few occasions where it is indicated during labor, and the extremely small dosage required at such times. Never should it be used in secondary inertia or to make good contractions stronger in order to strengthen the forces in a so-called tight fit. Individual responses vary tremendously, an abnormal response usually being evident with the first dose. The obstetrician, therefore, who orders the first dose over the telephone, is not present to assess the result and hence is unable to relieve uterine spasm or too violent contractions with anesthesia, and will sooner or later find himself in great difficulty with the mother or child. The dangers of Pituitrin are well known, but too often ignored, leading to tragedies such as here reported.

Failure to recognize relative disproportion in this multiparous patient was undoubtedly the chief cause of the rupture. What more comforting information could this obstetrician have had than the knowledge that one of the five babies had weighed 11½ pounds. What better example could we have of the treacherous nature of relative disproportion in a multiparous patient. No matter what the size of the mother's pelvis, if the presenting part is big enough trouble will ensue. Here the disproportion was due to an unrecognized hydrocephalus, but in many cases it is just a bigger child than accommodated in previous labors. The size of a woman's pelvis never changes, but the size of her children may show a tremendous variation, making the difference between easy and impossible delivery. It must be emphasized that multiparity in itself does not necessarily mean easy delivery. If obstetricians generally could rid themselves of the sense of well-being that comes with the knowledge one is dealing with a multipara and take the same care to make an accurate diagnosis as they do with their primiparas, the incidence of spontaneous rupture of the uterus, uncommon though it is, would be still further reduced.

Manipulative Rupture.—This term is used rather than traumatic rupture, to draw closer attention to the fact that this accident occurs during an obstetrical maneuver, which the obstetrician has elected to carry out and for which he must be prepared to take full responsibility. The cases comprise the largest group in any series, and in our own represent nine out of fifteen. Three of these reached us after manipulation had been carried out and rupture had occurred. These are marked with an asterisk in the table.

All patients were multiparous. In five the difficulty arose with the second baby, the others varying up tc the tenth pregnancy. In only one was there a history to indicate previous difficulty, and here an 8½ pound baby was born in an intervening pregnancy without trouble. One patient was only 22 years of age; six were over 38 years. It would seem that the degree of multiparity was not a particularly important factor.

Age might be of some significance, but from so small a series no worth-while conclusion can be drawn.

The indications for operative interference and the method used, together with the result to the fetus, are shown in Table II.

TABLE II. MANIPULATIVE RUPTURE, 9 CASES

INDICATION FOR MANIPULATION	NO. OF CASES	OBSTETRICAL MANEUVER RESULTING IN RUPTURE	FETAL MORTALITY	WEIGHT IN POUNDS
Disproportion	2	High forceps	Stillborn	10-8½
		Version and breech extraction	Alive and well	12-8
*Occiput posterior	1	Manual rotation	Stillborn	?
Hydrocephalus	2	Version and breech extraction	Stillborn	6-12
		*Version and breech extraction	Stillborn	9
Transverse presentation	2	Version and breech extraction	Stillborn	?
		Version and breech extraction	Stillborn	7
Frank breech	1	Breech extraction	Stillborn	10-4
*Face presentation	1	Version and breech extraction	Stillborn	9-8
			Fetal mortality 88%	

*Rupture occurred before admission.

The fetal mortality is extremely high, even if one omits the two cases of hydrocephalus. In seven, the maneuver resulting in rupture was either version and breech extraction or breech extraction alone. The indications varied, as could be expected, but, in seven out of the nine cases, an alternative method might have been indicated at some time during the labor.

The procedure used in treatment of the rupture, the length of time elapsing before diagnosis, and the result for the mother are shown in Table III.

TABLE III. MANIPULATIVE RUPTURE, 9 CASES

TREATMENT	NO. OF CASES	TYPE OF RUPTURE	WHEN DIAGNOSED	NO. OF CASES	PUERPERIUM	END RESULT
Porro section	2	Complete	During delivery	1	Fever, distention	Recovered
		*Complete	During delivery	1	Incontinent 14th day	Vesicovaginal fistula
Conservative treatment	7	Incomplete		2	Fever, distention	Recovered
		Incomplete			Fever, distention	Recovered
		*Complete	48 hours' delay	3	Moribund	Died
		Incomplete			Peritonitis	Died
		Incomplete			Fever, distention	Vesicovaginal fistula
		*Complete	4 days delay	1	Moribund	Died
		Incomplete	1 week delay	1	Mass in side	Recovered
						Maternal mortality 33⅓%

*Ruptured before admission.

Whether a rupture is complete or incomplete is of some importance, but should influence treatment only to a small degree. A complete rupture is usually more extensive and higher up, producing much more rapid and definite symptoms. The diagnosis is likely to be made and operation performed at once. In incomplete rupture the symptoms appear later and are those of a spreading hematoma in the extraperitoneal tissue, which may not be evident until some time after delivery, and then the temptation is to wait. Occasionally it is good

judgment to treat incomplete ruptures conservatively, but the hematoma may be enlarging posteriorly without our knowledge and the optimum time of operation may be missed. There is also the danger that the hematoma may burst through into the peritoneal cavity higher up, carrying with it the danger of peritonitis if the hematoma should become infected, as many of them do. Here there were five incomplete ruptures, all treated conservatively with one death. All of them had a very stormy puerperium with vomiting, distention, and fever. Of the four complete ruptures two were subjected to Porro sections and recovered, two were treated conservatively and died, their complete rupture being confirmed at autopsy. When rupture has occurred, the greatest single factor in influencing treatment will be the length of time that has elapsed before the diagnosis is made, and it is undoubtedly this time factor that has led to so much conservative treatment, as shown above. It is generally agreed that the proper treatment is immediate operation, but delay in diagnosis deprives us of this opportunity due to fear of infection, forcing us into being conservative.

As early diagnosis is so important, it is surprising to note that in only four of these nine cases was the diagnosis made at the time of delivery, the others being from forty-eight hours to one week later. Several factors account for this. There is a common belief that uncomplicated labor will produce shock. Occasionally it may, but surely this must be very occasional, and if shock occurs even after difficult delivery, it should mean internal injury until this can be ruled out. The obstetrician should be careful not to content himself with the diagnosis of simple shock and miss a ruptured uterus. Failure carefully to examine this type of patient is the most important cause of delay in diagnosis. Whenever a patient shows shock or a delivery has been done in which injury to the lower uterine segment could have occurred, the whole of the uterus should be explored. To examine the cervix is not enough for one of the patients reported above had the cervix repaired while a rupture higher up was completely missed. The risk of introducing a sterile glove into the uterine cavity cannot be compared to that of leaving an unrecognized rupture.

It has been said that immediate operation is the treatment of choice. In most cases a hysterectomy will be indicated, but, in a few, it may be possible to repair the rent in the uterus. If this is decided upon, the operator should give careful consideration to the question of sterilization, which in many cases will be definitely called for. No operative procedure should be undertaken until the patient has been treated for and recovered from her shock. Plenty of blood should be available for use during the operation.

The cases that remain undiagnosed, either in or out of hospital, leave no choice. Supportive measures with penicillin and chemotherapy are the only alternative and a high mortality must be expected.

To summarize, there are nine cases of rupture of the uterus due to manipulation. In spite of treatment there is a maternal mortality of 33⅓ per cent and a fetal mortality of 88 per cent. Two of the mothers who recovered had vesicovaginal fistulas. Not a very impressive record, but again comparable to those published by Delfs and Eastman, who lost 50 per cent of the mothers and 80 per cent of the babies under similar conditions. The remedy for such figures lies in prophylaxis. Obstetricians must strive to become more skillful in avoiding the situations leading up to these terribly difficult deliveries. Version and breech extraction and breech extraction without version accounted for seven out of nine ruptures. It may be argued that these ruptures occurred in the most difficult versions encountered, and that many times it has been a useful maneuver. In answer to this, during the same twenty-year period, version and breech extraction (after seven months' gestation and not including a second twin) were attempted on fifty-two occasions. They resulted in one maternal death, an infant mortality of 63 per cent, and four ruptured uteri, and left two

of those who recovered with bad vesicovaginal fistulas. Surely the time has come to find a better solution, and it may well be asked if this example of obstetrical art could not be almost entirely discarded in favor of a slightly more frequent use of cesarean section. With the increasing safety of low cervical and extraperitoneal sections, together with the prophylactic use of penicillin and chemotherapy, it is felt we might become a little more radical in our treatment of such complications as transverse presentation with prolapsed arm, brow and high occiput posterior. In the past such cases have frequently been treated by version with its attendant hazards. If care is taken in selection and especially if an early diagnosis is made, the baby being alive, a low or extraperitoneal section offers safety for the child and surely less risk to the mother. It is advocated that we very cautiously become a little less conservative when confronted with these problems.

Rupture of the Scar.—

Rupture of the scar of a previous cesarean section comprises the second largest group in this and other reports. There were five cases during this period and these are shown in Table IV.

TABLE IV. RUPTURE OF THE SCAR, 5 CASES

	AGE	TYPE OF PREVIOUS SECTION	PREGNANCY AT TIME OF RUPTURE	INDICATION FOR ORIGINAL SECTION	LENGTH OF GESTATION	TREATMENT	RESULT	
							MOTHER	CHILD
1	41	Classical	6th	Placenta previa	At term in labor	Porro section	Recovered	Stillborn
2	31	Classical	5th	Placenta previa	Term, medical induction	Porro section	Recovered	Stillborn
3	29	Classical	5th	Contracted pelvis, 4 sections	5 months	Porro section	Recovered	Stillborn
4	31	Classical	2nd	Eclampsia	6 months	Repair, sterilization	Recovered	Stillborn
5	28	Classical	3rd	Contracted pelvis	8 months	Porro section	Recovered	Stillborn

All five mothers lived and all five babies died. One rupture occurred as early as the fifth month. This was in a patient who had four previous classical sections. One was in the sixth month, one in the eighth, and two during labor. The patients who are shown to have ruptured during labor had delivered three and four children, respectively, without difficulty. Their fourth and fifth deliveries were classical cesarean sections for placenta previa. When they came to term in the last pregnancy with this favorable history, it was decided to allow them to go into labor. One of them was even started by medical induction. Neither progressed very far before rupture occurred, and immediate hysterectomy was undertaken. Both babies were lost. It had not been common practice to allow patients with previous cesarean sections to go through labor even under favorable conditions. The dictum, "once a cesarean always a cesarean," had been strictly adhered to. However, at this time the feeling had begun to arise that this was a little too radical. It was felt that certain patients who, from their history, offered what appeared to be a fair margin of safety, should be very carefully selected and allowed to go through labor. These two cases were among those thought to be safe. Both previous sections were done in our own hospital, and both patients had uneventful convalescences. Both had normal easy births before the placenta previa. It would seem that if it were ever safe to avoid a second cesarean the conditions were favorable here, yet in both cases rupture

occurred, resulting not only in the loss of the baby, but also in the loss of the maternal uterus. There seems to be no way to assess the strength of a uterine scar, and no way to pick the patient who will go through labor safely. Again referring to Delfs and Eastman, a case is reported where rupture occurred during pregnancy after three normal deliveries following cesarean section. Recently in Toronto a private case was reported where rupture occurred before labor began, after one intervening normal delivery. With such records as these there seems to be no basis for a belief in the ability to decide which case should be allowed to go through and which should have a repeat section. The extremely small infant and maternal mortality in present-day elective section bring us to the inevitable conclusion that there should be no deviation from the rule, "once a cesarean always a cesarean." The optimum time for repeat section is probably two weeks before the expected date unless the baby is very large or the patient experiences tenderness and discomfort in the region of the old scar, when an earlier date should be chosen.

Most disconcerting is the fact that three of our patients ruptured during pregnancy. One as early as the fifth month and one in the sixth. In the case of the earlier one, the number of preceding sections may have been a factor, but the patient who ruptured at six months had only one previous pregnancy. Unfortunately, the data with regard to the site of implantation of the placenta was not accurate enough to present, but it is felt from personal observation in a few of these cases that if this occurs in part under the scar it must play a large part in weakening the wall. In one case placental tissue was observed growing through the old scar and extending beyond it under the peritoneum.

The most important observation to be made in these five cases is the fact that they all occurred when the previous operation was a classical section. There were no ruptures of scars in the low cervical section during pregnancy or labor. There were none in the ten cases reported from Johns Hopkins, and in a series reported by Tollefson there were only two out of eleven. The classical type of operation, then, is responsible for twenty-four out of twenty-six ruptures, if these figures are totaled. Fortunately the number of classical cesarean sections done is decreasing markedly, and its responsibility for this dangerous complication in subsequent pregnancies should be another deterrent in its use. It would seem that with the other well-known advantages of the low section there is no longer a place in obstetrics for the classical operation.

Summary and Conclusions

A group of fifteen cases of rupture of the uterus occurring in the Toronto General Hospital during the twenty year period, 1927 through 1946, has been studied and serves as a basis for clinical discussion.

Spontaneous rupture would occur much less frequently if pituitrin were used more wisely, and if obstetricians were more alert to the dangers of relative disproportion in multiparous patients. Slightly less conservatism with regard to cesarean section is advocated.

The number of manipulative ruptures with their extremely bad results could be materially reduced if the complication leading up to the manipulation were recognized earlier and cesarean section resorted to. Version and breech extraction are condemned, and where difficult manipulative deliveries have taken place the whole of the uterus should be explored. If rupture is found, transfusion and laparotomy should be resorted to at once.

"Once a cesarean always a cesarean" is undoubtedly the safest rule to follow. Any continued deviation will eventually result in the rupture of a scar, placing the mother's life in jeopardy and causing almost certain death for the child.

Due to the very high incidence of previous classical cesarean sections in any series of ruptures of a previous scar, low cervical section should be done exclusively whenever this operation is indicated.

711 Medical Arts Building

Discussion

DR. N. W. PHILPOTT, Montreal, Quebec.—Our results in Montreal are quite similar to those presented by the essayist. However, our incidence of patients with ruptured uterus is much less. For example, I have taken a ten-year period from 1937 to 1946, inclusive. There were 24,393 deliveries and there were eight cases finally diagnosed as ruptured uterus. This is an incidence of 1 in 3,000.

This lowered incidence is possibly due to the fact that we do not practice version and extraction except on rare occasions. With the exclusion of those cases in which the second twin is delivered by version, we average only about three versions per year for other indications. In the eight cases, two mothers died and three babies were lost.

One spontaneous rupture occurred in a primiparous woman of 32 years. Her pregnancy was complicated by multiple fibroids in the uterine wall. The membranes ruptured eight weeks before term and labor commenced immediately. After twelve hours of labor she developed acute lower abdominal pain followed shortly by signs of shock. Operation revealed a hemorrhage in the capsules of the fibroid with rupture at the junction of its lower portion with the uterine muscle.

The seven other cases were of the manipulative variety. There were three cases following previous cesarean operation. Another interesting case was one where a craniotomy had been performed at the patient's previous confinement; at that time she went into shock and could easily have experienced an unrecognized rupture in the lower segment. Nine years later she was delivered by cesarean before the onset of labor. At this time there was an extensive rupture under the bladder.

The other three cases were: first, a disproportion case where high forceps were used; second, a breech with hydrocephalus which ended fatally for the mother; third, an extraordinary case in which the resident tried to induce labor by simple rupture of the membranes. This patient drained fluid for seven days but no labor was effected. Careful examination revealed two openings in the cervical canal. Operation revealed a false passage with extensive hemorrhage under the bladder. This opening had been made artificially by the instrument used to rupture the membranes. The amniotic sac was found to be intact.

One case was incorrectly diagnosed as ruptured uterus but autopsy examination revealed a most interesting condition. A multiparous woman, para xi, delivered an 11 pound infant. This was accomplished only after midforceps were employed, as well as excessive pressure on the fundus to aid in the delivery of the shoulders. Immediately following delivery the patient went into shock from which she never recovered. Two hours later she died. Naturally we thought that the operative delivery with excessive pressure on the fundus had caused a uterine rupture. The autopsy examination revealed an intact uterus but there was a ruptured aortic aneurysm accompanied by massive hemorrhage which was the cause of death.

I should like to emphasize those recommendations as stated in the paper. All shock should be effectively treated post partum. If the response is insufficient relative to the treatment received, then further investigation is essential. A vaginal examination should be made to exclude concealed hemorrhage, rupture of the uterus, or an inversion of the fundus.

This latter condition has occurred five times in the same ten-year period; there were three incomplete types and two were complete inversions. One case unfortunately was not recognized and the patient died of shock. Treatment of a ruptured uterus should be active. This is one time when blood transfusion in adequate quantity immediately followed by operation is a life saver.

DR. J. R. VANT, Edmonton, Alberta.—From a pathologist's viewpoint one must always keep in mind the possibility of infection in the uterine wall and try to determine the presence of infection early in the pregnancy. Rupture of the anterior or posterior wall is not nearly as serious as rupture of the lateral wall of the uterus. Infection means a weakened wall with an increased possibility of rupture.

Reynolds, F. Neon: Trilene as an Analgesic in Labour, Brit. M. J. 1: 537, 1949.

An account of the investigation into the possible use of Trilene by midwives as an analgesic in labour has been issued by the Royal College of Obstetricians and Gynaecologists. The study is based on 1,168 patients.

Efficacy is such that adequate relief can be given in a high proportion of cases, 76 per cent to 89 per cent, without any special skill upon the part of the administrator.

No evidence was adduced of any adverse effect upon length of labor, forceps rate, or obstetrical interference rate.

In the group to which Trilene alone was given there was one maternal death, a rate of 0.86 per 1,000, and that on the fourth day of the puerperium in a patient with mitral stenosis. In marked contrast the death rate was more than doubled, 1.96 per 1,000, in the group to whom no analgesic or anesthetic of any sort was given.

Fetal distress occurred in three cases among 1,168 in which nothing else but Trilene was given.

Some degree of asphyxia neonatorum occurred in 3.9 per cent of babies where Trilene alone was used, but a considerably higher proportion was noticed if Pethidine had been administered previously.

There were 25 stillbirths, again among 1,168 patients, but in no case was the analgesia considered in any way responsible. This gives a stillbirth rate of 21.4 per 1,000. In a series of 2,040 patients to whom no analgesia or anesthetic of any sort was given the stillbirth rate was 71.56 per 1,000. The final conclusion was that there was no evidence to show that Trilene influenced the stillbirth rate in any way.

The final conclusions are:

1. The limits of variation of the Trilene vapor air mixture delivered by the apparatus are far too great.

2. Under less ideal conditions or by deliberate misuse these limits can be caused to vary still further.

3. As a result of the above and also due to varying tolerance in different individuals, cases will occur where the mother will pass beyond the stage of cooperative analgesia into a state of uncooperative stupor. This has occurred in the best of hands, and in the case of less skilled supervisors this condition might easily be taken to a state of anesthesia.

R. GORDON DOUGLAS.

A NEW VIEW ON THE USE OF DICUMAROL IN THE PREGNANT PATIENT*

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THIS is a report of a preliminary study of anticoagulant therapy administered to a number of pregnant women presenting a history and/or evidence of venous disease. As the series developed the procedure evolved of administering Dicumarol earlier and earlier in the puerperium until the present regime of predelivery administration of Dicumarol was established.

It is admitted that embolic phenomena account for a very small percentage of maternal fatalities. Indeed, they are rare. Everyone has seen the patient, however, who, as a reminder of her pregnancy, is burdened with a chronically swollen, uncomfortable, or even painful leg due to phlebitis. It was the hope in commencing this study that a form of treatment using an anticoagulant might be evolved whereby these morbid conditions might be prevented.

Preliminary discussions with others regarding the advisability of the use of Dicumarol during the last trimester, during labor, or in the immediate postpartum period gave considerable concern. One eminent authority gave us to understand that in his considered opinion such use of anticoagulants would be a most dangerous procedure as blood loss would most likely be quite marked and possibly uncontrollable. There has been a great deal written on the indications for the use of anticoagulants in the treatment of venous disease. However, following a résumé of a considerable number of articles, one was impressed with the fact that there was almost total absence of any reference to thrombophlebitis or phlebothrombosis or their complications in the pregnant patient. This is in spite of the fact that Allen, Barker, and Hines[1] state that in the United States thrombophlebitis occurs after 0.4 to 1 per cent of deliveries.

Fortunately, venous thrombosis has its origin most frequently in the leg. In fact, 95 per cent of emboli, other than those of cardiac origin, arise in the veins of the lower leg. Many cases remain local and heal, some being recognized and some not. Those that do not heal may progress in one of two ways:

1. The thrombus may spread rapidly through deep venous channels to the groin giving rise to obstruction with acute symptoms of severe pain and swelling. Ninety per cent of femoro-iliac thrombophlebitis begin in this way. Because of deep vein thrombosis chronic swelling of the extremity may be expected.
2. Oschner's phlebothrombosis or quiet thrombosis may develop. There may be a minimum of signs or symptoms until pulmonary embolism occurs. Usually, however, if looked for, tenderness of the calf muscle may be elicited;

*Presented at the Third Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Quebec, Canada, Sept. 29 and 30, 1947.

Homan's sign is positive; there may be slight edema of the ankle, cyanosis of the foot when standing, and dilatation of the superficial veins. There is a slow propagation of the clot which floats free at its proximal end. The longer the floating clot the greater the likelihood of breaking from its mooring.

Thrombophlebitis is more common after difficult delivery, instrumental delivery, cesarean section, in cases where puerperal sepsis is or has been present, and in the presence of varicose veins. Therefore, in recommending a treatment it is assumed that the usual prophylactic measures, namely: Trendelenburg position, active exercise of limbs while in bed, deep respirations, correction of anemia and dehydration, and especially early ambulation,[2] will be instituted also in all these cases.

The majority of cases of postpartum thrombophlebitis probably occur from the third to the seventh day following delivery, although definite statistics could not be found. If this is true, then it is felt that if dicumarolization as a prophylactic measure in the puerperium is indicated, the earlier, following the delivery, that the patient is adequately dicumarolized, the safer it will be for that patient. Our experience has been that the administration of the initial dose of Dicumarol at the onset of labor does not produce the complication generally expected of this drug, namely, the possible increase in loss of blood.

Since embolus follows on thrombosis it is obvious that anticoagulation must be obtained as soon as possible, preferably before any thrombosis has occurred. We would suggest that an anticoagulant ought to be given at once when there is any sign of venous thrombosis and also when an embolus occurs. This is an attempt to prevent further venous thrombosis and pulmonary embolism and to lessen the possibility of resultant chronic venous insufficiency in the leg. We would go farther than this to recommend that it should be routinely administered, barring a definite contraindication, when there is a history of previous thrombosis or embolism, because of the increased probability of further venous thrombosis or embolism; especially when there is a toxic condition during pregnancy, or when there is any severe trauma or infection during labor.

Dicumarol, as a prophylactic and therapeutic agent, is superior in all ways but one to heparin. Dicumarol requires twenty-four to forty-eight hours to exert its effect; therefore, there is a lag in obtaining the desired result. Conversely, heparin, which exerts its effect almost immediately, has an advantage over dicumarol when embolism occurs suddenly. We have been content to use heparin only during the lag period of Dicumarol in the presence of an embolus. In all other instances, because of heparin's cost, we have used Dicumarol. Treatment formerly consisted of the recognized conservative measures plus Dicumarol, all being started as soon as possible after the onset of a venous complication. However, our chief object has been to ward off thrombosis and embolism so that we have administered Dicumarol earlier than has been done elsewhere. It must be understood, however, that we have most rigidly adhered to the routine of dicumarolization as outlined repeatedly by Allen and associates[1, 3] of the Mayo Clinic, the actual administration of Dicumarol being the sole responsibility of the internist. This routine is of such importance that we refer you to their works rather than discuss it briefly here.

The problem presented by a 31-year-old woman aroused our interest as to the possibility of preventing venous complications in the immediate postpartum period. This patient had had thrombophlebitis with basal pulmonary infarct at six months' gestation in her previous pregnancy. She was delivered at term and had pelvic thrombophlebitis in the immediate postpartum period. Throughout the interpartum period the legs were swollen and there was soreness of the veins. During the present pregnancy she suddenly, at three months' gestation, developed acute thrombophlebitis accompanied by bilateral basal infarction of the lungs. Her condition was such that operative procedures were considered ill advised. Dicumarol and heparin were administered with good results. Two months later there was an acute flare-up in the veins of the same leg. She was hospitalized, administered heparin and Dicumarol, and both saphenous veins were ligated. There was no subsequent edema but the veins remained tender. As the patient approached term we felt radical measures were indicated to prevent any further complications. Consequently at the onset of labor she was given 300 mg. of Dicumarol. Labor was short and relatively easy. The following day 200 mg. of Dicumarol were given and adequate dicumarolization was maintained for 10 days. There was no abnormal postpartum bleeding either immediate or delayed. She was allowed up on the first postpartum day. There was no morbidity and very little discomfort in the leg, which permitted discharge from hospital on the ninth postpartum day.

One of us (C. J.) was presented with the problem of treating two patients, each of whom had developed pulmonary emboli within twenty-four hours postoperatively. One had had a therapeutic abortion at a time when the veins in the left calf were tender. The other had had an abdominal hysterectomy with no apparent venous complication.

These cases prompted us to enquire concerning the experience of others regarding the safety of early administration of anticoagulants. Dr. Kvale, of the Mayo Clinic, encouraged us to continue giving Dicumarol, when indicated. We were also encouraged by the conclusions of Barnes and Ervin.[4] They reported that in normal pregnant patients administered 300 mg. Dicumarol during labor and 200 mg. each day of the first two days post partum, a determination of blood loss showed no significant difference between controls and the patients given Dicumarol. Also, there was no relation between the amount of blood loss and the prothrombin values. Furthermore, an observation by Dr. Segard, Director, Wisconsin Medical Research Foundation, that dicumarolization had no effect on the amount of menstrual flow, seemed sufficient justification to become more radical in the administration of Dicumarol.

The case of a young woman, para 0, gravida ii, who developed an acute thrombophlebitis of the left superficial saphenous in the upper two-thirds of the thigh at thirty-six weeks, was instructive. She was immediately admitted to hospital and, along with conservative treatment, was dicumarolized. The signs and symptoms of thrombophlebitis having entirely cleared within seven days, the patient was allowed up and on the ninth day was allowed to go home, her prothrombin level being 34 seconds (the normal being 18 to 20 seconds). She was given Dicumarol and instructed that two days later she was to take another 200 mg. This she did and one hour later membranes ruptured spontaneously, labor began, and the patient returned to hospital. She had a fairly rapid labor being delivered by low forceps with no abnormal bleeding. The patient was allowed up on the first postpartum day. Her legs felt normal and they have not given her any trouble since; there have been no tenderness, no swelling, and no soreness of veins or discoloration.

A young woman, 34 years of age, para i, gravida iii, presented an interesting complication. During the first pregnancy she was forced to wear elastic stockings due to marked varicosities. Throughout the present pregnancy she did not wear stockings, although she had been instructed to do so. At approximately eight and one-half months

she developed acute thrombophlebitis of the upper and middle third of the thigh down to the knee with extension across the anterior aspect of the upper leg. She was immediately admitted to hospital, put on complete bed rest, continuous heat, sedation, with elevation of the foot of the bed and Dicumarol therapy started. Three days later all signs and symptoms of the thrombophlebitis had disappeared, but the patient was kept dicumarolized. On the eleventh day in hospital the patient was administered 200 mg. of Dicumarol, prothrombin level being 30 seconds. The following morning the left saphenous vein was ligated. Twelve hours later membranes ruptured spontaneously, the patient went into labor and after six and one-half hours she was delivered by low forceps. She had a retained placenta which had to be removed manually. Throughout this procedure and the postpartum course there was no abnormal bleeding. On the second postpartum day, while the patient was still dicumarolized, the right saphenous vein was ligated. On her fourth postpartum day she was allowed up and was discharged from hospital on the ninth postpartum day. This patient was seen less than one week ago at which time she claimed there was no discomfort in the leg whatsoever. On examination the veins were not swollen, nor tender, nor was there any evidence of edema. These two patients, though delivered while adequately dicumarolized, exhibited no evidence of any abnormal postpartum bleeding, nor evidence of further venous complication.

Considering the report of Barnes and Ervin and the observations of Dr. Kvale and Dr. Segard, as previously quoted, together with our own experience, we discussed the advantages to be gained from administration of Dicumarol before venous complications arose. We decided to become more and more radical. Now, when the indications mentioned above are present, we do not hesitate to give 300 mg. Dicumarol with the first labor pain and continue adequate dicumarolization from then forward for at least ten days post partum. We have, in fact, had several patients adequately dicumarolized for an acute thrombophlebitis when labor began. Operations, such as curettement, cesarean section, and manual removal of retained placenta, have been done with the patient in a similar state of adequate dicumarolization. In none has abnormal bleeding or any other complication attributable to Dicumarol been observed.

Fifteen patients have been delivered to whom Dicumarol had been given at the onset of labor, or who were adequately dicumarolized at time of delivery. In extreme brevity we propose to indicate the complications of six representative patients and your attention is drawn to the question marks which each has presented. The protocol of six of these cases follow:

CASE 1.—A woman, aged 33 years, para iii, gravida iv, had a history of marked varicosities in both legs with occasional mild attacks of thrombophlebitis for a period of five years. She wore elastic stockings during the two preceding pregnancies as well as the present one. Ligation of veins was advised but patient refused. She was delivered of twin boys after twelve hours of labor.

What were her chances of thrombophlebitis or even emboli following delivery? Should the multiple pregnancy influence treatment? We felt the possibilities of venous complications were sufficient to justify immediate administration of Dicumarol on admission to hospital in labor.

CASE 2.—A woman, aged 31 years, para i, gravida ii, gave a history of marked varicosities of vagina and vulva since her first pregnancy three years ago. She had to travel 27 miles to hospital after onset of labor. She was delivered by low forceps one-half hour after admission, a total of three hours' labor.

This patient presented the picture of possible increased risk due to traumatic injury to blood vessels of pelvis where there was the combination of varicosities of the vagina with rapid descent of the fetal head, aggravated by a rapid, fairly long drive to hospital.

CASE 3.—The patient was a para ii, gravida iii, aged 34 years. She gave a history of discomfort in the legs due to varicosities following her first pregnancy, four and one-half years ago. During the second pregnancy three years ago she wore elastic stockings but was quite uncomfortable. One year later she had the veins injected. Labor began spontaneously and she was delivered after three and one-half hours by low forceps.

When varicosities, though previously injected, return during pregnancy, should they be ligated or would Dicumarol at onset of labor be adequate treatment?

CASE 4.—The patient, aged 24, para ii, gravida iii, had a history of acute thrombophlebitis in the left leg on the tenth postpartum day with a previous pregnancy eleven months ago. During the present pregnancy the leg was swollen and uncomfortable. After eleven hours in labor she was delivered by transverse cervical cesarean section on account of shoulder presentation.

Should this patient—with a definite history of previous postpartum thrombophlebitis with a swollen, uncomfortable leg—have a vein ligation during the antenatal period? Would she have recurrence of thrombophlebitis? She had a cesarean section eleven hours after administration of Dicumarol yet no evidence of any abnormal bleeding.

CASE 5.—The patient was 37 years of age, para i, gravida ii, with a history of varicosities during her first pregnancy. In the present pregnancy she had thrombophlebitis of the right leg at six and one-half months. She was admitted to hospital, dicumarolized, and the right saphenous vein ligated. She was readmitted at eight and one-half months with pre-eclampsia. Following four days of conservative treatment without definite improvement labor was medically induced. Dicumarol was administered just prior to the initiation of the medical induction. Labor lasted three and three-fourth hours and she was delivered by low forceps.

Our problem here was a history of varicosities, and acute thrombophlebitis with vein ligation during the present pregnancy with moderately severe pre-eclampsia which did not respond to conservative treatment. Should we dicumarolize her during treatment for pre-eclampsia or at onset of labor?

CASE 6.—The patient was a 39-year-old, para ii, gravida iii, with a history of postpartum thrombophlebitis appearing on the second postpartum day with a previous pregnancy four years ago. At six months during the present pregnancy she developed acute thrombophlebitis of the left leg. She was hospitalized and adequately dicumarolized. Following subsidence of signs and symptoms, bilateral ligation was performed. She had a return of thrombophlebitis at eight and one-half months. Dicumarol therapy was started at home, her prothrombin level being known, and on the evening of the second day she was admitted to hospital. When adequate dicumarolization had been attended, a medical induction was started. The response was rapid and the patient delivered seven hours later by manual rotation of a persistent posterior followed by low forceps.

Our problem was to protect this patient from further complications immediately before labor, intrapartum, and immediately post partum. Due to domestic conditions immediate hospitalization was impossible so treatment was initiated at home.

Each patient was allowed up on her first postpartum day and was discharged from hospital not later than the ninth postpartum day. There was no evidence of any abnormal bleeding either at the time of delivery or during the puerperium. There were no signs or symptoms of any further venous complications. All patients, except one, have been checked postnatally at approximately six weeks, giving a history of either very slight discomfort or no discomfort of the involved leg, and no cases of swelling or edema.

Comment

It is hoped that the facts just presented will be sufficient to arouse the interest of those who are concerned with trying to prevent patients from suffering the sequelae of venous complications of pregnancy and that they will also

investigate this form of treatment and mode of administration. As a result of our studies we are convinced that the results from anticoagulation therapy are dramatic in the prevention and treatment of venous thrombosis and embolism. We agree with those workers who feel these conditions are almost entirely preventable.

We do not, for instance, yet know whether all pregnant women obviously facing labor with a thrombophlebitis should have prophylactic venous ligation. It seems to us that this procedure has carried those patients, in whom we have had it performed, much more comfortably throughout their pregnancies as well as obliterated a large area from which an embolus might arise. We have not, however, had this procedure done primarily to help prevent embolus but rather as straight therapeutics for their varicose veins. We are concerned when a patient has thrombosis about the eighth month (or at any stage in pregnancy) whether or not she should be dicumarolized from then until she is up and about following her delivery. True, this is impractical and most inconvenient but still thrombophlebitis and embolism are all this and often fatal.

It is our belief that any patient who during the gestational period demonstrates acute phlebothrombosis or thrombophlebitis should be hospitalized and treated by anticoagulant therapy, i.e., Dicumarol; that such a patient, as well as any pregnant patient who has or has had a history of venous disease, may with safety be given 300 mg. Dicumarol immediately following onset of labor and that she should be kept dicumarolized for at least ten days following delivery.

We are so convinced of its value that any patient who has had a venous complication during her pregnancy, where no contraindication to its use is present, is given 300 mg. Dicumarol to take home with her. When we are called at the onset of labor she is advised to take this dose before leaving for the hospital.

Conclusions

1. Fifteen patients have been delivered, to whom Dicumarol had been administered at the onset of labor or who were adequately dicumarolized at the time labor commenced.

2. Dicumarol, properly administered, can be safely used ante partum, during labor, or post partum.

3. There is no increase in immediate or delayed bleeding from the pregnant uterus due to the use of Dicumarol.

4. Dicumarolization will probably decrease the incidence of pulmonary emboli in pregnant women with venous disease.

5. The proper use of Dicumarol will markedly decrease the number of women with painful, swollen legs arising from venous complications of pregnancy.

Grateful appreciation is hereby acknowledged to the director and technicians of the serological laboratory for their cooperation and interest.

References

1. Allen, Barker, and Hines: Peripheral Vascular Diseases, Philadelphia, 1946, W. B. Saunders Company, pp. 730-738.
2. Collins, Conrad G., and Nelson, Edward W.: Am. J. Obst. & Gynec. **52**: 946-957, 1946.
3. Allen, Edgar V.: J. A. M. A. **134**: 323-329, May 24, 1947.
4. Barnes, Allan C., and Ervin, H. K.: Surg., Gynec. & Obst. **83**: 528-530, 1946.

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Discussion

DR. THOMAS PRIMROSE, Montreal, Quebec.—I am a hematologist and some of my work in the past and present has been in the use of Dicumarol. I regard Dicumarol as being an extremely dangerous drug and I do not agree with Dr. Adamson that Dicumarol can be taken at home by the patient. Three hundred mg. is quite a large dose and when giving dosage as large as this one must have a report from the laboratory on the blood prothrombin level every three or four hours. In our laboratory we feel that 300 mg. is quite probably a safe dose as far as bleeding goes but we have had one patient who bled very heavily from mucous membranes when the prothrombin time was only about 45 seconds. Our method of controlling Dicumarol dosage is to give the drug with prothrombin level estimation every four to six hours for the first day or two of dosage until we find how the individual patient reacts to the drug. There was one patient in the Royal Victoria Hospital recently in the surgical ward who was given 300 mg. of Dicumarol and this sufficed to put the prothrombin time up to 300 seconds. The patient nearly died from bleeding that was extremely difficult to control. I would suggest that a much safer prophylactic regime against thrombosis would be by the repeated dosage of heparin. The effect of heparin wears off very quickly and overdosage can be rapidly controlled. Sometimes after the administration of 300 mg. of Dicumarol it will take about ten days for the prothrombin time to return to normal. I would be very much afraid to use the dosage of Dicumarol suggested on the antepartum patient.

DR. W. G. COSBIE, Toronto, Ontario.—I believe that there is a great risk of embolism when an obstetrical patient has varicose veins. In a recent article by Allen of the Mayo Clinic it was shown that the likelihood of pulmonary embolism is increased when the patient has varicose veins and when there have been previous emboli.

DR. ADAMSON (Closing).—I can quite frankly say that I have appreciated the discussion that has taken place. We do not know whether this contribution is going to be of value in the treatment of our pregnant patients or not, but I am rather of the opinion that it may be. I think I should have included indications and methods of administering Dicumarol which have been described by members of the Mayo Clinic. Dicumarol is given to the patient to take home but we do not feel that we are being quite as radical as it may appear since the prothrombin time for the individual has been determined before giving her Dicumarol. The prothrombin time is checked daily. Since it has been shown that the use of 65 mg. of Synkavite (synthetic vitamin K) intravenously can control the Dicumarol effect very rapidly, we have not been worried about the use of Dicumarol instead of heparin. However, in our series of cases we have had no necessity to use Synkavite for the control of an excessively prolonged prothrombin time.

PREGNANCY AND PULMONARY TUBERCULOSIS*

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THIS investigation of pregnancy and pulmonary tuberculosis reviews the cases treated conjointly at the Royal Victoria Montreal Maternity Hospital and the Royal Edward Laurentian Hospital (M.D.) from Jan. 1, 1935, until Aug. 1, 1946.

There is a natural division of the subject into three groups:

TABLE I

A. Pregnancy in inactive pulmonary tuberculosis	54 cases
B. Pregnancy in active pulmonary tuberculosis	33 cases
C. Therapeutic abortion in pregnancy and pulmonary tuberculosis	30 cases
Total	117 cases
Total corrected	110 cases

There were seven patients who have records in two of the above groups so that the review deals with 110 individuals.

The follow-up in thirty-three other cases of pregnancy with pulmonary tuberculosis was incomplete and these were discarded. Four cases of extra-pulmonary tuberculosis with an associated pregnancy were also excluded.

TABLE II

Total number of cases of pregnancy and pulmonary tuberculosis	143
Total number of deliveries from Jan. 1, 1935 to Aug. 1, 1946	23,192
Incidence of pulmonary tuberculosis among the pregnancies delivered	0.61%
The accepted incidence of pulmonary tuberculosis among women of childbearing age is approximately	1.5%

In the absence of routine radiographic examinations of the chests of the antenatal patients we can make no comment on our low incidence.

The stages of the pulmonary lesion are shown in Table III.

TABLE III

STAGES OF PULMONARY LESION	UNILATERAL	BILATERAL	
Minimal pulmonary tuberculosis (Stage I)	28	15	39%
Moderately advanced tuberculosis (Stage II)	7	37	40%
Far-advanced pulmonary tuberculosis (Stage III)	1	22	21%

Suffice it to say that the patients received as adequate treatment as possible when the pulmonary condition was recognized and they were supervised with added care at the antenatal clinic. The treatment followed the recognized modern methods and lack of hospital beds and, rarely, lack of cooperation of the patient were the restricting factors.

*Presented at the Third Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Quebec, Canada, Sept. 29 and 30, 1947.

The follow-up in the living cases averaged forty-eight months and one year was taken as the minimum period.

TABLE IV. END RESULTS OF ALL CASES

Died	18	16.3%
Active disease present	21	19.1%
Inactive disease	71	64.6%

Pregnancies with inactive pulmonary tuberculosis and those with active was taken as the minimum period.

TABLE V

PREGNANCY IN INACTIVE PULMONARY TUBERCULOSIS				PREGNANCY IN ACTIVE PULMONARY TUBERCULOSIS			
Cases	54			Cases	33		
Parity:							
Primiparas	29	53.7%		Primiparas	20	60.6%	
Multiparas	25	46.3%		Multiparas	13	39.4%	
No. of babies born			76	No. of babies born			36

Antenatal complications were unimportant in each group.

Premature labor resulting in the birth of a baby of 2,500 Gm. or less occurred in six cases in the inactive group, 8.2 per cent, and in eight cases in the active group, 25 per cent. Five of these active cases were moderately advanced; three were far advanced and very ill. The incidence of premature labor in the hospital is 5.7 per cent. It is thus evident that these patients have a predisposition to premature labor.

TABLE VI. STAGE OF PULMONARY LESION

	UNILATERAL	BILATERAL		UNILATERAL	BILATERAL	
I.	18	12	55.5%	5	1	18.2%
II.	4	13	31.5%	1	14	45.4%
III.	1	6*	13 %	0	12	36.4%

*All postthoracoplastics.

The extent of the lesion was more advanced in the active group, 81.8 per cent being in the Stages II and III groups.

The method of delivery is tabulated in Table VII.

TABLE VII

PREGNANCY IN INACTIVE PULMONARY TUBERCULOSIS				PREGNANCY IN ACTIVE PULMONARY TUBERCULOSIS			
TYPE OF DELIVERY, 76 BABIES				TYPE OF DELIVERY, 36 BABIES			
Spontaneous		52	68.4%	Spontaneous		24	66.6%
Forceps		14	18.4%	Forceps		8	22.2%
Low forceps	13			Low forceps	5		
Midforceps	1			Midforceps	3		
Breech extraction		0		Breech extraction		1	
Cesarean section		10	13.2%	Cesarean section		2	5.5%
Classical section				Classical with ligation of the tubes			
With sterilization	4						
No sterilization	3						
Low segment section							
With sterilization	1						
No sterilization	2						

Medical or surgical induction was used only if an obstetrical indication was present.

The first stage was allowed to proceed with adequate sedation.

The total forceps incidence is 23.1 per cent, while the forceps incidence for the hospital is 26 per cent.

The incidence of cesarean section was 10.7 per cent, but in only five cases was the indication solely the pulmonary condition. The incidence of section in the hospital is 5 per cent.

Third stage abnormalities are presented in Table VIII.

TABLE VIII

PREGNANCY IN INACTIVE PULMONARY TUBERCULOSIS		PREGNANCY IN ACTIVE PULMONARY TUBERCULOSIS	
Postpartum hemorrhage	5 cases	Postpartum hemorrhage	4 cases
Incidence	6.5%	Incidence	12.1%
Incidence in general for all deliveries 0.77%			

In this series there was a definite predisposition to have an abnormal third stage.

TABLE IX

PREGNANCY IN ACTIVE PULMONARY TUBERCULOSIS			PREGNANCY IN ACTIVE PULMONARY TUBERCULOSIS		
Type of Anesthetic Given.—			*Type of Anesthetic Given.—*		
Inhalation type	57	71.1%	Inhalation type	11	30.5%
Nitrous oxide and oxygen	22		Nitrous oxide and oxygen	3	
Nitrous oxide and oxygen with ether	23		Nitrous oxide and oxygen with ether	2	
Nitrous oxide and oxygen with local	2		Nitrous oxide and oxygen with cyclopropane	2	
Chloroform	10		Chloroform	4	
Noninhalation type	20	25.2%	Noninhalation type	19	52.8%
Local	14		Local	18	
Spinal	6		Spinal	1	
None given	2	2.5%	None given	5	14 %
Not recorded	1	1.2%	Not recorded	1	2.1%

Inhalation anesthesia was used in a higher proportion of these cases than one would expect, but the trend in the active group was to give a local or spinal anesthetic.

The puerperium and morbidity rates are described in Table X.

TABLE X

PREGNANCY IN INACTIVE PULMONARY TUBERCULOSIS			PREGNANCY IN ACTIVE PULMONARY TUBERCULOSIS		
Puerperium.—			*Puerperium.—*		
Morbidity	7	12.9%	Morbidity	17	51.5%
Intrauterine infection	6		Intrauterine infection	4	
Pyelitis	1		Intrauterine infection with pulmonary TB.	4	
			Pulmonary TB.	9	
Incidental Data.—			*Incidental Data.—*		
Blood transfusions given		5	Blood transfusions given		7
Postpartum pneumothorax refills done		4	Postpartum pneumothorax refills done		7

The incidence of morbidity in general was 19.2 per cent.

(The standard of morbidity for these cases was one rise to 100.6° F. excluding the first twenty-four hours.)

The figures are self-explanatory.

No pneumoperitoneum therapy was used in the cases under review.

No streptomycin was administered to any patient while under observation in the Royal Victoria Montreal Maternity Hospital.

TABLE XI

PREGNANCY IN INACTIVE PULMONARY TUBERCULOSIS			PREGNANCY IN ACTIVE PULMONARY TUBERCULOSIS		
Babies born*		76	Babies born*		36
Neonatal deaths		3	*Neonatal deaths*		1
Erythroblastosis fetalis 6th day postpartum	1		Second of twins. Prematurity with atelectasis and intracranial hemorrhage 6th day post partum	1	
Multiple congenital anomalies 4th day post partum	1				
Multiple congenital anomalies 15th day post partum	1				
Later deaths reported		2	*Later deaths reported*		2
Tuberculous meningitis 2 months post partum	1		Congenital heart disease at 3 months	1	
Tuberculous meningitis 6 months post partum	1		Tuberculous meningitis at 3 years	1	

*The babies were all born alive in both groups.

TABLE XII

PREGNANCY IN INACTIVE PULMONARY TUBERCULOSIS			PREGNANCY IN ACTIVE PULMONARY TUBERCULOSIS		
Weight of Babies.—			*Weight of Babies.—*		
Premature (1 only 985 Gm.)	9	2075 Gm.	Premature	11	1795 Gm.
Term	67	3013 Gm.	Term	25	3059 Gm.

Except for the neonatal deaths noted, the babies did well and the premature babies' progress was especially gratifying.

While most of these babies had patch tests and were kept under observation, nothing of significance was noted in the data obtained.

The subsequent course of the cases after delivery in the inactive pulmonary tuberculosis was as follows:

TABLE XIII. INACTIVE PULMONARY TUBERCULOSIS

Remained inactive	48 cases	86.4%
Became active	6 cases	13.6%

Two cases became active after rapidly repeated pregnancies, but are now inactive. Both had therapeutic abortions during their reactivation. Three are still active.

One woman died thirteen years after her first pregnancy and within two years of a therapeutic abortion for her third pregnancy.

In the active pulmonary tuberculosis the subsequent course is shown in Table XIV.

TABLE XIV. ACTIVE PULMONARY TUBERCULOSIS

Became inactive	8 cases	24.2%
Remained active	12 cases	36.4%
Died	13 cases	39.4%

Sixteen had been under treatment for chest lesion prior to pregnancy; all except one were moderately or far advanced. Of these, two cases became inactive; four cases remained active; and ten patients died. Fifteen cases were diagnosed shortly before and during the pregnancy and two were diag-

nosed in the immediate puerperium. Seven of these had minimal lesions and the remaining ten moderately or far advanced. Of these, six cases became inactive; eight cases remained active; and three patients died.

No patient died during the antenatal period, during labor, or in the first ten days post partum.

Discussion

In the inactive pulmonary tuberculosis group the patient has been under supervision and the disease is a known entity. The patient has been drilled in self-care and discipline which she maintains to a greater or less degree depending on home conditions, her intelligence, and the desire to cooperate.

Under continued supervision a single pregnancy will not affect the course of the disease adversely, but repeated pregnancies at close intervals with the related task of child rearing may result in activation of the disease.

With the active pulmonary tuberculosis group this is true to a less extent.

The phthisiologists are of the opinion that pregnancy is but an incident in the course of the disease, but the statement may be qualified by the following observations:

1. If with rest and successful collapse therapy the disease is rendered inactive, the prognosis is good (especially if this be achieved prior to the onset of the pregnancy).

2. If the pulmonary condition is not well controlled with the above measures the prognosis is poor.

3. If the pulmonary condition be other than minimal and it is not diagnosed or treated during pregnancy, the prognosis is grave.

Early diagnosis is most important, but, as shown by other authors and by a small group in this series, patients with pulmonary tuberculosis do not appear early in their pregnancies for supervision. Routine radiographic examination of the chest in the antenatal clinic has proved its value but the ultimate would appear to be routine chest radiological examination of all women of childbearing age at regular intervals.

There is one point to add with respect to the management of the baby after delivery. The use of BCG vaccine to immunize the baby during the first months of life is a practical procedure. The Swedish workers consider that the child who becomes tuberculin positive after the administration of the vaccine acquires an immunity which enables him to resist infection provided he is not unduly exposed to tuberculosis.

Therapeutic Abortion in Pregnancy With Pulmonary Tuberculosis

This procedure, which was once the accepted treatment of pregnancy and tuberculosis, still has a restricted usefulness.

In cases treated in sanatoria under the optimum conditions of supervision and therapy the phthisiologists have all but excluded it from their scheme of management. However, in most large gynecological units therapeutic abortions are being performed with pulmonary tuberculosis as the medical indication. The Margaret Hague Hospital is a notable exception.

The material consists of thirty patients who had therapeutic abortions because of associated pulmonary tuberculosis.

The incidence in relation to all deliveries is 1.25:1,000.

The incidence in relation to all cases of pulmonary tuberculosis in pregnancy is 27.2 per cent.

TABLE XV. COMPARISON OF THE INCIDENCE OF THERAPEUTIC ABORTIONS FOR PULMONARY TUBERCULOSIS TO ALL DELIVERIES IN FIVE LARGE HOSPITALS

Bellevue	1935-1940	6.5:1,000	1941-1946	6.1:1,000
Johns Hopkins	1896-1934	2.8:1,000		
Chicago Lying-in Hospital	1931-1939	1.2:1,000		
New York Lying-In Hospital	1932-1943	0.65:1,000		
Margaret Hague Hospital	1931-1939	0		
With 1.25:1,000 we strike a middle course.				

If the period is divided into two approximately equal periods it is shown that there is a slight increase in the incidence of the therapeutic abortions in recent years at the Royal Victoria Montreal Maternity Hospital:

1935-1940	1.07:1,000
1941 to August, 1946	1.4:1,000

This is due to the increased number of cases of pulmonary tuberculosis.

The decision to abort was made by the head of the department after consultation with the phthisiologist and the gynecologist in charge of the case. There are no hard or fast rules but the basic principle followed was that there be present a chance that the chest disease could be brought under control by treatment.

Sterilization was considered if there was a social-economic factor as well.

The stage of the pulmonary lesions is shown in Table XVI.

TABLE XVI. STAGE OF PULMONARY LESION

STAGE	UNILATERAL	BILATERAL		
I	8	3	36.7%	(3 inactive)
II	2	13	50.0%	(3 inactive)
III	0	4	13.3%	(1 inactive) (postthoracoplasty)

In the active cases the stage of the lesion was moderately advanced or far advanced in 50 per cent of the cases as compared to 80.8 per cent of the active full-term group.

The follow-up of the cases extended over a period of from one to ten years with the average being forty-seven months.

The end results obtained are shown in Tables XVII and XVIII.

TABLE XVII

INACTIVE PULMONARY TUBERCULOSIS, 7 CASES		ACTIVE PULMONARY TUBERCULOSIS, 23 CASES	
Died	0	Died	5 21.7%
Now active*	1 14.3%	Still active	6 26.1%
Still inactive	6 85.7%	Now inactive	12 52.2%
The death rate including both groups 5 cases 16.6%			
The time interval that elapsed between operation and death:			
0-1 year		2 deaths	
1-2 years		0 deaths	
2-3 years		3 deaths	

*The patient whose case is now active had two full-term pregnancies one and five years after the therapeutic abortion.

The administrative time lapse while consultation and decision to operate were being considered was noted to be considerable.

TABLE XVIII

Parity.—		
Primiparas*	11	36.7%
Multiparas	19	63.3%
Duration of Pregnancy.—		
4 weeks	1	
6 weeks	4	
8 weeks	9	
10 weeks	10	
12 weeks	5	
14 weeks	2	

*One primipara was evacuated on two occasions.

TABLE XIX. TYPE OF OPERATION

Dilatation and evacuation		21
Dilatation and evacuation, two stage		5
With pack in cervix	3	
With bag induction	2	
Hysterotomy with sterilization		4
Subtotal hysterectomy		1

TABLE XX. TYPE OF ANESTHETIC GIVEN

Inhalation		12	31.6%
Nitrous oxide and oxygen	4		
Nitrous oxide and oxygen with ether	3		
Nitrous oxide and oxygen with cyclopropane	2		
Nitrous oxide and oxygen after Avertin	3		
Noninhalation*		26	68.4%

*At the present time intravenous or spinal anesthesia is used in almost 100 per cent of gynecological operations.

With the modern operative procedures no untoward shock, hemorrhage, or infection was encountered and the subsequent course of the patients did not indicate that the operation aggravated the pulmonary condition.

Pneumothorax refills were given postoperatively to three patients.

Thirteen children were born to these mothers subsequently, ten of whom were by then in an inactive phase, but two still had active disease present.

Comment

In this series there is a higher salvage rate than obtained by Bridgman and Norwood. This is possibly due to the improvement in operative and anesthetic technique.

With Active Disease.—The far-advanced cases do not deviate from their downward course and might better be left alone and tuberculosis therapy instituted as practical. This is at variance with some authorities.

The moderately advanced cases must be considered on an individual basis and in special ones therapeutic abortion may improve the prognosis. No dogmatic statement is permissable.

The minimal cases are similarly qualified.

With Inactive Disease.—The inactive cases do well, but they do equally well if allowed to proceed to term under supervision.

In recent years the social-economic factor with the strain of home duties has been given more careful consideration, but this by itself has not been the indication for operation in any case in this series.

Summary

One hundred seventeen cases of pregnancy and pulmonary tuberculosis in one hundred ten individuals were reviewed.

Of the fifty-four patients with inactive pulmonary tuberculosis, six, or 13.6 per cent, became active, but there is nothing to prove that they would not have become reactivated in any event.

Of the thirty-three patients with active pulmonary tuberculosis, 75.8 per cent were either dead or still had active disease present and 24.2 per cent were inactive.

Of the thirty patients who had therapeutic abortion, 40 per cent were dead or still active and 60 per cent were inactive. If only the active cases are considered, the figures are 47.8 per cent and 52.2 per cent.

These results when compared with the previous statement are surprising, but no conclusions are drawn at this time. The two groups were not identical as to stage of disease.

The forceps rate did not deviate greatly from the forceps rate for the hospital generally.

Premature labor occurred in 13.3 per cent of the cases as compared to the general figure of 5.7 per cent. The babies were all born alive and the incidence of neonatal deaths was not appreciably increased.

The third stage was abnormal in 9.5 per cent of the cases.

Conclusions

Pregnancy in inactive pulmonary tuberculosis will cause reactivation, of serious importance, in very few patients.

Pregnancy with active pulmonary tuberculosis will cause the patient's condition to grow worse in direct proportion to the stage of the lesion and the degree of control that can be achieved.

Therapeutic abortion still has a limited place in the treatment of pregnancy with pulmonary tuberculosis.

The management of the pregnant patient with pulmonary tuberculosis requires very close cooperation between the phthisiologist and the obstetrician and their efforts are restricted by the lack of accommodation for these patients.

The more widespread use of BCG vaccine to produce an immunity in the neonatal period may lead to a greater salvage rate of children born of mothers with pulmonary tuberculosis.

Our present routine practice is to send babies born of mothers with pulmonary tuberculosis directly from the case room for B.C.G. vaccination.

We wish to acknowledge the aid given to us by Dr. N. W. Philpott and Dr. Hugh Burke and the cooperation of our colleagues in the follow-up of certain of the cases.

Discussion

DR. BRIAN D. BEST, Winnipeg, Manitoba.—In the Province of Manitoba, the trend in teaching at present is to treat the tuberculosis and ignore the pregnancy in the vast majority of cases. Pregnancy, in our opinion, does not aggravate pulmonary tuberculosis. It either has no effect or is actually beneficial. We feel the salutary effects are the result

of the upward pressure on the diaphragm which acts somewhat like a double phrenicotomy, the improved general metabolism and increased weight, and the natural tendency of the woman, as her pregnancy advances, to reduce her activities automatically.

It is in the puerperium and during the first year or two following delivery that the greatest danger lies, as it is during this time that loss of sleep, strain, and anxiety associated with the care of the infant, etc., have their baneful effects. As it has been said, child-rearing is more harmful than childbearing so far as the tuberculous patient is concerned. It is established practice to obtain chest films as a routine in all prenatal patients.

DR. P. J. KEARNS, Montreal, Quebec.—Since 1928 in all cases of ectopic pregnancy at our clinic 5 cases have shown typical tubercles in the Fallopian tube. Furthermore, of all gynecological operations which we have done for so-called pelvic induration, we have found that 8 per cent showed tuberculosis. I believe that tuberculosis of the genital tract is quite possibly much more common than is generally believed.

DR. J. S. HENRY, Montreal, Quebec.—Fortunately for my patients I have seen very little tuberculosis of the genital tract. Recently I have been having x-ray chest films done on all my private patients. In the last 400 cases, eighteen have shown some evidence of tuberculosis. About half were definitely healed lesions which required no further attention. Four of the remaining nine showed probable activity of the tuberculous lesion and in two of these, following consultation with the chief of our department, therapeutic abortion was carried out. One aborted spontaneously and is still under the care of the phthisiologists. The fourth threatened to abort but did not do so and the lesion, whatever it was, is now arrested.

DR. G. J STREAN, Montreal, Quebec.—What Dr. Simpson's survey shows is very true. I would like to emphasize that these patients must have no inhalation anesthesia and that some substitute for the intra-abdominal pressure of pregnancy must be made quickly after delivery.

DR. SIMPSON (Closing).—I may say that the labors of most of these patients were quite easy and spontaneous delivery was completed in most instances. In answer to Dr. Grant, we are making it a practice to have a phthisiologist in consultation before and after the delivery of our patients and we rely on his judgment as to when pneumothorax should be instituted. It depends on the individual case but as a general rule the sooner the better. Dr. Kearns' figures were very interesting and only emphasize that tuberculosis of the genital organs is much more common than is generally believed.

Bueno, B.: Contribution to the Study of Large Ovarian Tumors, Toko-ginec. práct. **8**: 79, 1949.

The author describes the clinical history, gynecologic management, and pathology of a 26-kilogram ovarian cystadenoma ultimately removed successfully from a 36-year-old woman.

C. E. FOLSOME.

Original Communications

THE DATING OF OVULATION AND OTHER OVARIAN CRISES BY HISTOLOGICAL EXAMINATION IN COMPARISON WITH THE FARRIS TEST*

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THE observations in this paper represent the study of thirty-nine cases in which a test for ovulation by the method of Farris was done upon women who were about to be subjected to surgical exploration of the pelvis for therapeutic reasons, so that the occurrence of ovulation could be verified directly and its time in the cycle estimated by examination of ovarian and endometrial tissues removed at operation. The primary purpose of the study was to evaluate the Farris test, but, as we shall point out, it was actually a test of agreement of information gained by the several methods rather than a check upon a single method. Readers will perceive that the degree of congruence was found to be considerable, and that even certain discrepant cases proved in the end to yield significant information.

The women were patients at the University of Pennsylvania Hospital and at the Graduate Hospital of Philadelphia. They were made available for study through the courtesy of Drs. Carl Bachman and Robert A. Kimbrough, Jr., and their respective staffs, including Drs. Craig Muckle and Charles Freed, to all of whom our thanks are due for their interest and coperation. Through the courtesy of Drs. R. C. Horn, Jr., and E. A. Case, sections of endometria prepared in the pathological laboratories of the respective hospitals also were made available for study.

The Test for Ovulation.—Urine specimens collected by the patients at their homes before admission, or collected at the respective hospitals after admission, were subjected to the rat test at the Wistar Institute under the direct supervision of one of us (E. J. F.).

The test, described by Farris (1946a, 1946b), is based upon the observation that the urine of sexually mature women contains, during a period of about four days before ovulation, a gonadotrophic substance, presumably of pituitary origin, which produces a hyperemia of the ovaries of immature rats to which it is administered by subcutaneous injection.

The technique of the test is as follows: 2 c.c. of the urine which the patient passes on arising in the morning is injected subcutaneously into each of two immature female white rats of the Wistar strain. Each animal is killed

*Aided by a grant from the Samuel S. Fels Fund.

by illuminating gas, at the end of two hours. The abdomen is opened. The two ovaries are drawn, one at a time, into the wound, and the color of each is compared with the graded shades of red of the Munsell color system.

In the presence of normal ovulation, the patient's urine induces hyperemia in the ovaries of the rat for about four consecutive days, ovulation occurring on the last day of the reaction. In the total absence of ovulation, there is no hyperemia of the rat's ovary. If the ovulation process is abnormal, hyperemia occurs, but usually not on four consecutive days. Types of abnormal reactions have been described previously (Farris, 1948a).

Examination of the Ovaries.—Ovaries removed at operation were taken promptly to The Wistar Institute. Here Dr. W. H. Lewis noted surface conditions and measured sizes of ovaries, follicles, corpora lutea and corpora hemorrhagica produced by recent ruptures. Ova were aspirated from follicles, mounted in various media, and photographed. Attempts to fertilize them and to obtain cleavages were unsuccessful. Preliminary correlations were made between the conditions found in the ovaries and the conditions predicted by Dr. Farris. These will be presented in another paper.

The ovaries were prepared for Kodachrome photographic records of the entire organ before follicles were aspirated. Free hand sections of corpora lutea and corpora hemorrhagica were also photographed. The material was then preserved in 10 per cent formalin.

At the Department of Embryology, Carnegie Institution, the ovarian specimens were photographed in black and white, or sketched, and were searched for evidences of recent or impending ovulation. In many cases they were cut into slabs, a few millimeters thick, for examination under low powers of the microscope. Blocks were cut from all corpora lutea and other structures thought to be relevant to the dating of ovulation. These were sectioned and stained mostly by the paraffin-hematoxylin and eosin technique.

The dating of the ovulations was done by G. W. C., Sr., by collation of the gross and histological details in comparison with corpora lutea of known age. No detailed account of the day-to-day changes of the human corpus luteum has yet been published, although a good deal of information is in hand, notably in the publications of Brewer and Jones (1942, 1947, 1948), Papanicolaou, Traut, and Marchetti (1948) and Schroeder (1930), as well as in the unpublished material of A. T. Hertig of the Boston Lying-in Hospital and Free Hospital for Women, and of the Department of Embryology of the Carnegie Institution.

The dating used in the present investigation, therefore, rests largely, as far as documented evidence goes, on study of the rhesus monkey as set forth in a monograph by Corner, Sr. (1945), supplemented by some practical knowledge of human corpora lutea. Dr. Hertig kindly furnished his dating of a few specimens, and others were seen by Dr. James H. Graham and by Corner, Jr., when they were members of Hertig's staff. Essentially, however, the estimate of the age of a corpus luteum in the following protocols means that the section resembles that of the rhesus monkey of the corresponding day and its precision is subject to the same limitations that affected the dating of the rhesus corpora lutea. Such experience as we had before undertaking the present work indicated that the rate of organization of the human corpus luteum is closely similar to that of rhesus monkey.

The details found useful for dating the corpus luteum, i.e., characteristics of the lutein cells, theca interna, blood vessels, fibrin clot, and central connective tissue, are tabulated in the article cited (Corner, Sr., 1945). A few histological details that are useful in dating monkey corpora lutea do not ap-

pear consistently in human corpora, i.e., the inconspicuous state of the theca interna in the monkey from day 4 to day 10, and the conspicuous venous sinuses in the inner zone of the lutein wall from about day 7 on.

We are under the impression that our dating of the human corpus luteum by microscopic examination may be considered correct to the day, on the first day or two after ovulation; correct to the day, plus or minus one day, during the rest of the first week; and correct to the day, plus or minus two days, after about day 8.

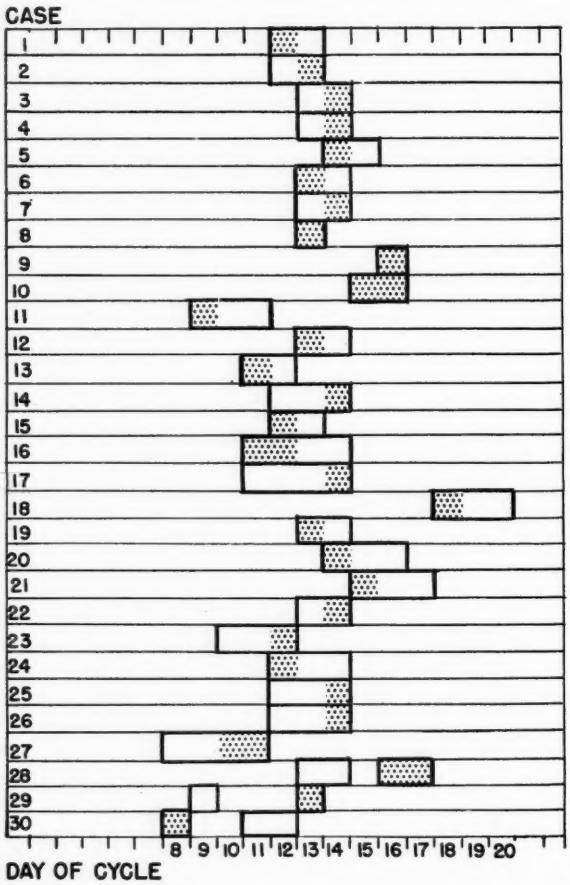

Fig. 1.—Tabulation of all thirty cases in which ovulation occurred, showing days on which ovulation was indicated, combining results of all three methods. Dots indicate day of ovulation by urine test.

Dating of the Endometrium.—In the past decade, a good deal of information has been obtained about details of the cyclic changes of the human endometrium, so that a section from the uterus can be assigned to its stage in the cycle with relatively certainty. A particularly valuable contribution by Hertig (1945) unfortunately is not readily accessible. The more recent atlas of the human female reproductive tissues by Papanicolaou, Traut, and Marchetti (1948) supplies useful information, as do the papers of Rock (1940) and Brewer and Jones (1942, 1947, 1948) cited below.

The dating of specimens in the present investigation was done by G. W. C., Jr., who has had the advantage of a year's experience with Hertig (1947-1948). Drs. Hertig and Graham have kindly seen and dated one or two of the slides.

In brief, the details used in determining the stage of the cycle at which a given specimen was obtained, include: the total thickness of the endometrium, the extent and form of the glands, the height of the gland epithelium, the position of the nuclei in epithelial cells, the presence and frequency of mitotic division, the presence and location of vacuoles, the amount of secretion in the glands, the occurrence and extent of pseudodecidual reaction,

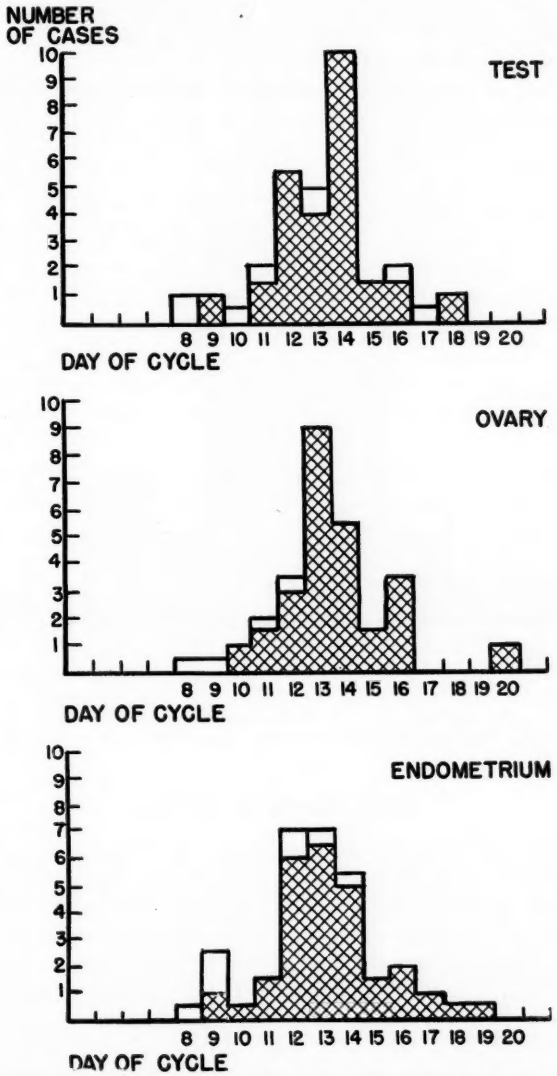

Fig. 2.—Frequency distribution by days of cycle, according to the three methods of estimation. Cases assigned to two possible days are drafted as a half unit on each of the two days. Shaded areas, twenty-four cases of groups A, B, C. White areas, four cases of groups D, E, F.

edema of the stroma, and the extent of the coiled arteries. The picture presented by the specimen, made up of these details, is compared with the standard day-by-day descriptions. For the sake of conformity, the stage of a given specimen is (in accord with the usual practice of gynecologists) referred to a standardized 28-day cycle, in which the day of onset of menstruation is designated day 1, ovulation being assumed to occur on day 14. The next menstrual

flow begins on day 29, which is also day 1 of the next cycle. In computing the dating in the present investigation, the stage of the endometrium was, whenever practicable, stated as of a given day following ovulation, including the day of ovulation in the count. The estimated day on which ovulation occurred was then calculated by subtraction. For example, if the operation was performed on day 18 of the cycle, and the endometrium was judged to be of day 6, ovulation was estimated to have occurred on day 13.

We believe that the accuracy of the estimate is approximately of the same order as that attainable in dating the corpus luteum. The assigned dating may therefore be considered correct to the day plus or minus one, e.g., an endometrium stated in the protocol to be of day 6 after ovulation may actually be of day 5 to 7.

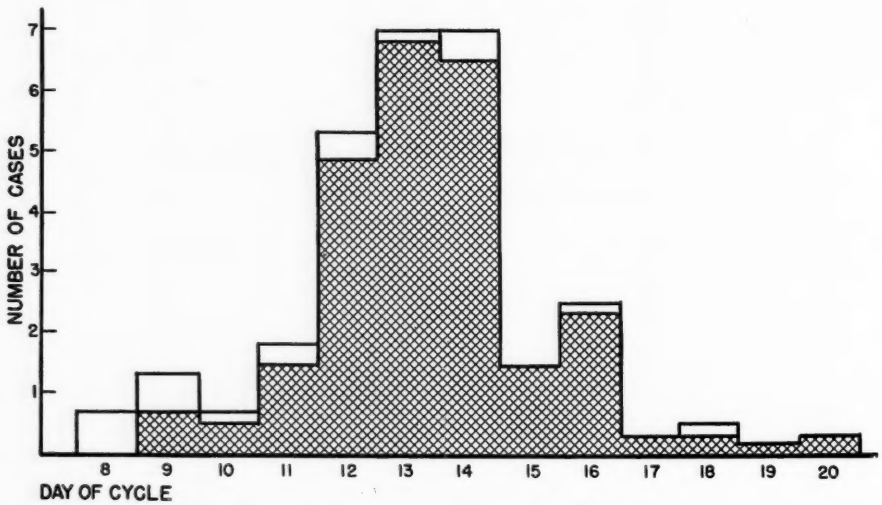

Fig. 3.—Frequency distribution of ovulation in cycle, plotted by averaging all three methods of dating. Cases assigned to two possible days are graphed as a half unit on each of the two days. Shaded areas, twenty-six cases of groups A, B, C. White areas, four cases of groups D, E, F.

Compilation of Results

In the following protocols the cases are grouped according to the degree of agreement between the dating of ovulation by the urine test, on one hand, and the histological examination of the ovaries and endometrium on the other. Such a grouping of course cannot be mathematically precise for several reasons. (1) The histological dating is, as already stated, not always accurate to a single day. (2) Datings from ovary and endometrium, respectively, do not always agree to the day, and a choice or an average must be taken. (3) The division of the cycle into 1-day blocks is artificial and gives rise to errors of as much as a half-day or more, because the critical events, i.e., onset of menstruation, ovulation, and operation occur at various hours during the day to which they are assigned.

The grouping therefore represents an arbitrary averaging of the findings, made for the practical purpose of displaying the results.

Protocols

The order and significance of the entries is as follows: number in this series; initials of name as in Wistar Institute records; number in Carnegie records (ovarian material); age of patient; diagnosis; nature of operation;

day of operation (op.) in the cycle; dating of ovulation by Farris test (Test); dating by estimation from the ovary, first citing the estimated day of age of the (c.l. d.) corpus luteum, then the calculated day of ovulation in the cycle (ov. d.); dating by estimation from endometrium, first citing the estimated stage as of the standard 28-day cycle (*st.c.d.*), then the calculated day of ovulation (ov. d.) in the patient's cycle.

The numbers of the hospital clinical records and the pathological records, including the slides of the endometria, are on file at both The Wistar Institute and the Carnegie Department of Embryology.

A. Datings Agree Within One Day (10 cases).—

1. O. C., 8413, age 43 years. Myoma uteri, endometrial polyp, chronic salpingitis, endometriosis right tube. Total hysterectomy, bilateral salpingo-oophorectomy. Op. d.16. *Test:* ov. d.12. *Ovary:* c.l. d.4, ov. d.13. *Endometrium:* st.c.d.17-18, ov. d.12-13.

2. He. Wi. 8437, age 36 years. Myoma uteri, chronic pelvic inflammatory disease. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.13. *Test:* ov. d.13 or mature follicle as yet unruptured. *Ovary:* c.l. d.1, ov. d.12. *Endometrium:* chronic endometritis; late proliferative stage, some evidence of high estrogen activity; compatible with day of ovulation, i.e., st.c.d.14, ov. therefore d.13.

3. S. G., 8440, age 34 years. Myoma uteri, chronic bilateral adnexitis. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.14. *Test:* ov. d.14. *Ovary:* c.l. d.1-2, ov. d. 13-14. *Endometrium:* chronic endometritis; late proliferative stage compatible with day of ovulation, i.e., st.c.d.14, ov. d.14.

4. A. M., 8489, age 42 years. Myoma uteri. Dilation and curettage. Total hysterectomy, right salpingo-oophorectomy. Op. d.15. *Test:* ov. d.14. *Ovary:* fragments of c.l. d.2, ov. d.14. *Endometrium:* st.c.d.16, ov. d.13.

5. W. H., 8491, age 33 years. Myoma uteri, left chronic adnexitis. Total hysterectomy, left salpingo-oophorectomy, excision c.l. right ovary. Op. d.19. *Test:* ov. d.14. *Ovary:* c.l. d.5, ov. d.15. *Endometrium:* chronic endometritis, st.c.d.18-19, ov. d.14-15.

6. V. C., 8495, age 41 years. Myoma uteri, left chronic salpingitis. Dilatation and curettage, total hysterectomy, left salpingo-ophorectomy. Op. d.18. *Test:* atypical, ov. d.13. *Ovary:* c.l. d.5-6, ov. d.13-14. *Endometrium:* st.c.d.18-19, ov. d.13-14.

7. V. S., 8513, age 35 years. Chronic pelvic inflammatory disease, fixed retroversion of uterus. Total hysterectomy, bilateral salpingo-oophorectomy. Op. d.14. *Test:* ov. d.14. *Ovary:* c.l. d.2, ov. d.13 (Fig. 6). *Endometrium:* late proliferative stage compatible with day of ovulation, i.e., st.c.d.14, ov. d.14.

8. H. C. 8531, age 37 years. Myoma uteri, chronic pelvic inflammatory disease. Total hysterectomy, bilateral salpingo-oophorectomy. Op. d.12. *Test:* ov. d.12, or unruptured follicle. *Ovary:* c.l. d.1, ov. d.12. *Endometrium:* late proliferative stage compatible with day of ovulation, i.e., st.c.d.14, ov. d.12.

9. S. T., 8546, age 31 years. Myomi uteri, chronic pelvic inflammatory disease. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.17. *Test:* ov. d.16. *Ovary:* c.l. d.2, ov. d.16. *Endometrium:* late proliferative stage compatible with day of ovulation, i.e., st.c.d.14, ov. d.16.

10. S. B., 8549, age 35 years. Myoma uteri, chronic pelvic inflammatory disease. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.22. *Test:* ov. d.15 or 16 (difficult case). *Ovary:* c.l. d.7, ov. d.16. *Endometrium:* superficial layer missing; st.c.d.20-21, ov. d.15-16.

B. Dating Agrees Within One Day but With Some Uncertainty Due to Greater Spread of the Datings Than in Group A, or to Imperfections of the Data (8 cases).—

11. N. B., 8420, age 28 years. Myomata uteri, chronic pelvic inflammatory disease. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.14. *Test:* abnormal reaction, ov. d.9. *Ovary:* c.l. d.4-5, ov. d.10-11. *Endometrium:* st.c.d.19, ov. d.9.

12. B. H., 8442, age 30 years. Myoma uteri, previous removal of both tubes and left ovary, follicle cyst right ovary. Dilatation and curettage. Subtotal hysterectomy. Excision follicle cyst, right ovary. Op. d.10. *Test:* day 1 of reaction, ov. expected d.13. *Ovary:* large follicle (9 mm. diameter), conjectured to be about 3 days before ovulation (Fig. 4). *Endometrium:* just past mid-proliferative stage, few days before ovulation.

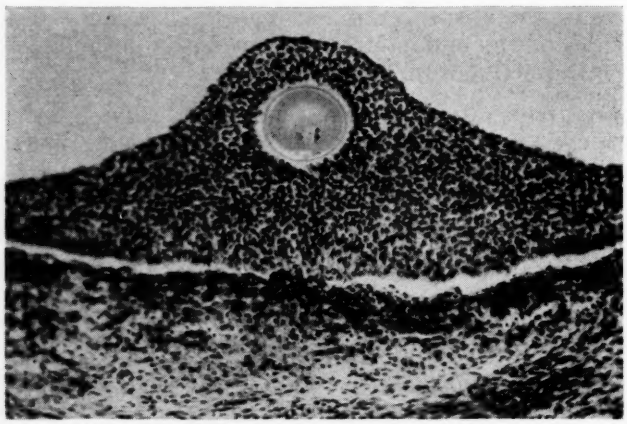

Fig. 4 (Case 12).—Part of 9 mm. follicle. (×100.)

13. M. G., 8443, age 44 years. Myoma uteri, cystic degeneration left ovary. Dilatation and curettage, left salpingo-oophorectomy. Op. d.14. *Test:* abnormal reaction, ov. d.11. *Ovary:* c.l. d.3-4, ov. d.11-12. *Endometrium:* very unsatisfactory curettings, st.c.d.16, ov. d.12.

14. R. S., 8457, age 37 years. Myomata uteri, chronic pelvic inflammatory disease. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.15. *Test:* ov. d.14. *Ovary:* c.l. d.2, ov. d.14. *Endometrium:* poor specimen, st.c.d.16-17?, ov. d.12-13?

15. A. H., 8474, age 37 years. Myomata uteri. Left ovary previously removed. Total hysterectomy, right salpingo-oophorectomy. Op. d.14. *Test:* ov. d.12. *Ovary:* c.l. d.2, ov. d.13. *Endometrium:* st.c.d.15-16, ov. d.12-13.

16. N. H., 8508, age 45 years. Dysfunctional uterine bleeding. Total hysterectomy, bilateral salpingo-oophorectomy. Op. d.15. *Test:* ov. d.11-12. *Ovary:* c.l. poorly preserved, ov. d.13-14? *Endometrium:* st.c.d.17-18, ov. d.11-12.

17. R. B., 8548, age 30 years. Myomata uteri, chronic pelvic inflammatory disease. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.20. *Test:* ov. d.14. *Ovary:* c.l. d.7-8, ov. d.13-14. *Endometrium:* no surface epithelium, chronic endometritis, st.c.d.22-23?, ov. d.11-12?

18. E. J., 8550, age 44 years. Myoma uteri, chronic pelvic inflammatory disease. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.25. *Test:* atypical, ov. d.15 or 18. *Ovary:* c.l. d.6, ov. d.20. *Endometrium:* st.c.d.20-21, ov. d.18-19.

C. Dating Differs by One Day (8 cases).—

19. B. He., 8419, age 37 years. Myomata uteri, bilateral ovarian endometriosis. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.16. *Test:* series of specimens incomplete; ov. d.13? *Ovary:* c.l. d.3, ov. d.14. *Endometrium:* st.c.d.16, ov. d.14.

20. H. A., 8439, aged 36 years. Cystocele, rectocele, chronic right adnexitis. Dilatation and curettage, plastic repair, right salpingo-oophorectomy. Op. d.16. *Test:* ov. d.14. *Ovary:* c.l. (poorly preserved fragment) d.1-2, ov. d.15-16. *Endometrium:* poorly prepared tissue, late proliferative stage, compatible with ovarian findings, i.e., st.c.d.14-15, ov. d.15-16.

21. E. F., 8473, age 29 years. Myoma uteri. Total hysterectomy, bilateral salpingectomy, excision follicle cyst left ovary. Op. d.19. *Test:* ov. d.15. *Ovary:* c.l. d.4, ov. d. 16, *Endometrium:* surface epithelium missing, st.c.d.16, ov. d.17.

22. R. C., 8506, age 34 years. Myoma uteri, chronic pelvic inflammatory disease. Dilatation and curettage, subtotal hysterectomy, left salpingo-oophorectomy, right salpingectomy, excision c.l. right ovary. Op. d.15. *Test:* ov. d.14. *Ovary:* c.l. d.3, ov. d.13. *Endometrium:* st.c.d.16, ov. d.13.

23. L. R., 8514, age 52 years. Myoma uteri. Total hysterectomy, bilateral salpingo-oophorectomy. Op. d.16. *Test:* ov. d.12. *Ovary:* c.l. d.6-7, ov. d.10-11. *Endometrium:* Poor preparation, st.c.d.19-20, ov. d.10-11.

Fig. 5.

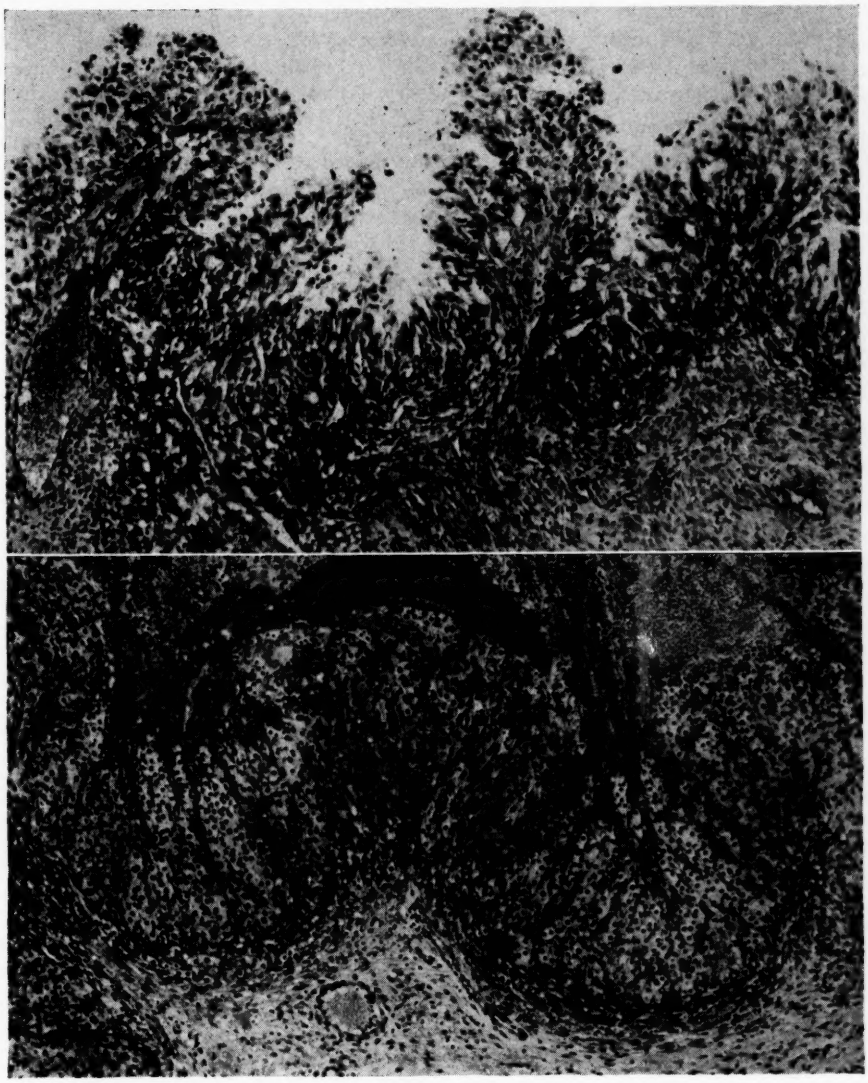

Fig. 6.

Fig. 5 (Case 26).—Corpus luteum about 1 day old. (Other parts of the same corpus luteum were slightly more advanced.) (×75.)
Fig. 6 (Case 7).—Corpus luteum about 2 days old. (×75.)

24. M. Co., 8533, age 34 years. Pelvic inflammatory disease, with bilateral hydrosalpinx; pelvic endometriosis. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.19. *Test:* ov. d.12. *Ovary:* c.l. d.6-7, ov. d.13-14. *Endometrium:* st.c.d.20, ov. d.13.

25. M. Ca., 8588, age 38 years. Myoma uteri, chronic pelvic inflammatory disease. Total hysterectomy, bilateral salpingo-oophorectomy. Op. d.16. *Test:* ov. d.14. *Ovary:* c.l. d.4-5, ov. d.12-13. *Endometrium:* st.c.d.17-18, ov. d.12-13.

26. F. T., 8589, age 36 years. Dysfunctional uterine bleeding, previous uterine suspension. Subtotal hysterectomy, right salpingectomy, left salpingo-oophorectomy. Op. d.14. *Test:* ov. d.14 or unruptured follicle. *Ovary:* c.l. d.2, ov. d.13 (Fig. 5, taken from the least advanced part of the corpus luteum). *Endometrium:* (variable picture) st.c.d.16, ov. d.12.

D. Dating Differs by Two Days (1 case).—

27. E. J., 8586, age 38 years. Myoma uteri, multiple pelvic adhesions. Previous removal of tubes and right ovary. Subtotal hysterectomy, left oophorectomy. Op. d.13. *Test:* incomplete, ov. d.10-11. *Ovary:* c.l. d.5-6, ov. d.8-9. *Endometrium:* chronic endometritis, evidence of chronic metrorrhagia, st.c.d.18-19, ov. d.8-9.

E. Dating Differs by Three Days (1 Case).—

28. L. C., 8587, age 31 years. Myomata uteri, follicle cyst right ovary. Total hysterectomy, right salpingo-oophorectomy. Op. d.17. *Test:* abnormal reaction, ov. d.16-17. *Ovary:* no ovulation (evidently the ovary containing c.l. was not removed). *Endometrium:* definitely postovulational, st.c.d.17-18, ov. d.13-14.

F. Dating Differs by Four Days (2 cases).—

29. L. S., 8392, age 37 years. Myoma uteri, subtotal hysterectomy, left salpingo-oophorectomy. Op. d.15. *Test:* ov. d.13. *Ovary:* no ovulation (evidently the ovary containing c.l. was not removed). *Endometrium:* definitely postovulational, st.c.d.20, ov. d.9.

30. T. Y., 8407, age 34 years. Myomata uteri. Subtotal hysterectomy, right salpingo-oophorectomy, ruptured follicle in right ovary noted on opening abdomen. Op. d.12. *Test:* ov. d.8. *Ovary:* spontaneously ruptured follicle damaged by operative handling, or mature follicle ruptured at operation; ovum retained in follicle. If natural rupture it was less than 48 hours old. If ov., d.11 or 12. *Endometrium:* late proliferative stage compatible with day of ovulation (st.c.d.14) or with large follicle and high estrogen level before ovulation. If ov., d.12.

G. No Ovulation, Agreed by All Three Methods (3 cases).—

31. M. Cr., 8478, age 42 years. Myoma uteri, subacute bilateral tubo-ovarian abscesses. Bilateral ovarian endometriosis, subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.14. *Test:* atypical, large follicles, no ovulation. *Ovary:* large follicle in early atresia. *Endometrium:* late proliferative, compatible with large follicle.

32. M. M., 8510, age 42 years. Myomata uteri, chronic adnexitis. Total hysterectomy, bilateral salpingo-oophorectomy. Op. d.14. *Test:* abnormal reaction, no ovulation detected. *Ovaries:* no ovulation. *Endometrium:* poor material, late proliferative stage.

33. V. J., 8562, age 35 years. Myoma uteri, pelvic inflammatory disease. Total hysterectomy, right salpingo-oophorectomy. Op. d.7. (cycle history unsatisfactory). *Test:* no ovulation. *Ovary:* no ovulation. *Endometrium:* proliferative stage.

H. Retrogression of Large Follicle, With Positive Test (6 cases).—

34. Ha. Wi., 8410, age 35 years. Pelvic inflammatory disease. Total hysterectomy, bilateral salpingo-oophorectomy. Op. d.12. *Test:* abnormal reaction; ov. d.12. *Ovaries:* a large hemorrhagic follicle with atypical "luteinization" of wall. *Endometrium:* mid- to late proliferative stage.

35. A. L., 8421, age 42 years. Myomata uteri, pelvic inflammatory disease. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.11. *Test:* abnormal reaction; ov. d.11. *Ovaries:* large collapsed follicle with patches of unluteinized granulosa over "luteinized" theca interna (Fig. 7). *Endometrium:* late proliferative stage with evidence of hyperestrinism.

36. G. B., 8476, age 41 years. Myoma uteri, cystocele. Plastic repair, total hysterectomy, right salpingo-oophorectomy. Op. d.15. *Test:* ov. d.14. *Ovary:* large collapsed hemorrhagic follicle with retrogressing granulosa over "luteinized" theca interna (Fig. 8). *Endometrium:* late proliferative stage.

37. R. L., 8481, age 37 years. Myomata uteri and adenomyosis uteri, chronic salpingitis. Dilatation and curettage, subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.13. *Test:* abnormal reaction; ov. d.11. *Ovaries:* Large collapsed follicle with retrogressing granulosa over "luteinized" theca interna. *Endometrium:* mid-proliferative stage.

Fig. 7.

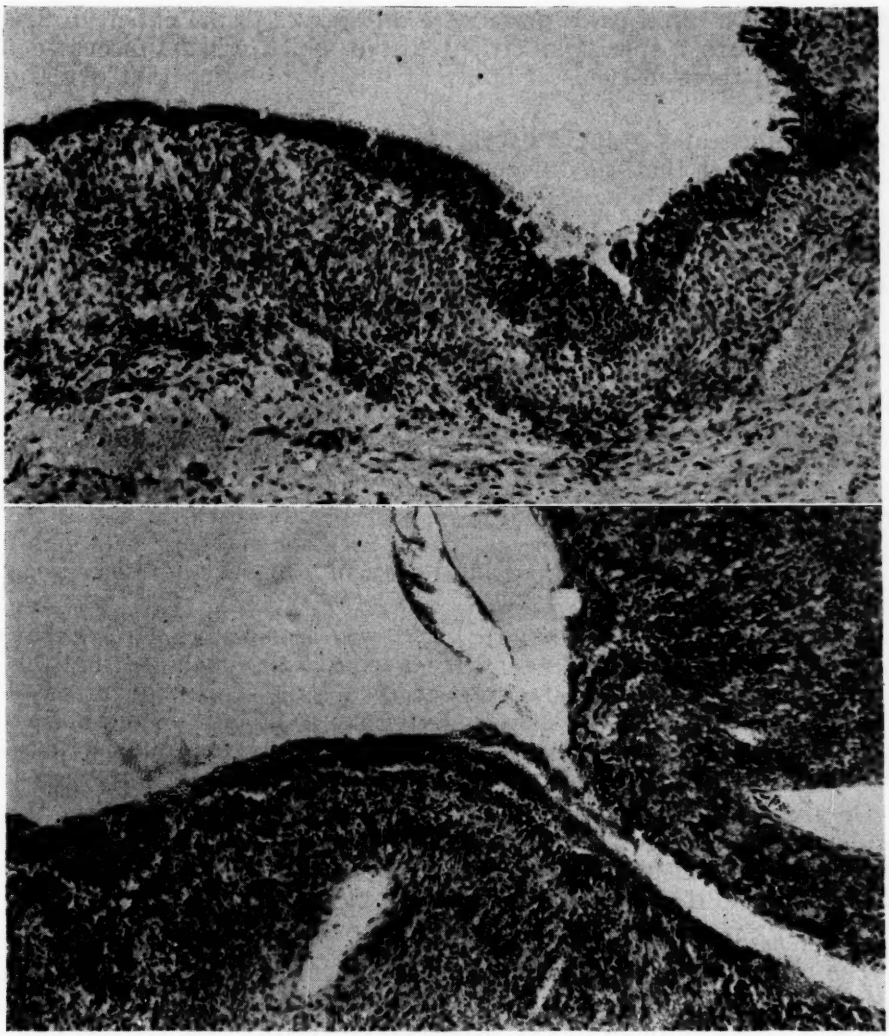

Fig. 8.

Figs. 7 (Case 35) and 8 (Case 36).—Retrogression of large follicles with positive ovulation test. In Fig. 7, Case 35, the granulosa is largely preserved with much hypertrophy of the theca interna. In Fig. 8, Case 36, the granulosa is mostly lost. (Both ×75.)

38. H. Wh., 8482, age 35 years. Myomata uteri, bilateral salpingitis, pelvic inflammatory disease. Subtotal hysterectomy, bilateral salpingo-oophorectomy. Op. d.13. *Test:* ov. d.12. *Ovaries:* large collapsed follicle with some "luteinization" of the theca interna. *Endometrium:* mid- to late proliferative stage.

39. A. B., 8585, age 45 years. Myomata uteri. Total hysterectomy, bilateral salpingo-oophorectomy. Large follicle ruptured during operation. Op. d.13. *Test:* abnormal reaction, ov. d.12. *Ovaries:* large hemorrhagic follicle with "luteinized" theca interna, presumably artificially ruptured. *Endometrium:* late proliferative stage.

Discussion

Critique of the Congruence of the Data.—

Summarizing the foregoing 39 protocols, there were 30 cases (groups A to F) in which ovulation occurred. In 26 of these, the dating by the urine test agreed with the histological dating within one day or with a difference of only one day. In 4 cases there were differences to the extent of 2, 3, or 4 days. In 6 cases a special situation existed which will be discussed below. In 3 cases all three methods of study agreed in declaring that ovulation did not occur.

Fig. 1 illustrates graphically the data of the 30 protocols of groups A to F. It will be seen that the differences of one to four days between the dating by urine and by histological observation, respectively, are not constant in their direction on the graph; in other words, there is no systematic tendency for the urine test to indicate ovulation earlier or later than the histological dating. This is what would be expected if the two methods indicate the same event, with an inherent uncertainty of a day or two in either method of dating, due to physiological variability and to difficulties of judgment.

It is obvious, as we have hinted above, that the logical procedure followed in this investigation is not like that of laying a foot-rule against something to be measured. Our scales for datng ovulation by histological examination of the ovary and the endometrium are themselves in need of verification. The comparison actually made here is therefore of a kind often necessary in biological work, in which two or more related physiological states, each varying at unknown or insufficiently known rates, are compared with one another. If a high degree of congruence is observed, the plausibility of each of the measurements is strengthened.

The degree of agreement reported here is evidently much greater than could have been produced by chance, and it may safely be concluded that the urine test will indicate the time of ovulation in a high proportion of cases with sufficient accuracy for clinical use. Extensive pragmatic evidence of the reliability of the test has been obtained already in a large number of cases of artificial insemination (Farris, 1948, and other data as yet unreported).

On the other hand, the high order of agreement also reflects the very considerable understanding of the histology of the primate cycle that has been gained by histologists and pathologists in recent decades by study of the human being and the rhesus monkey.

Frequency Distribution of Ovulations.—

The present series, although small, is unique in its dating of ovulation by three distinct methods.

Fig. 2 presents plots of the frequency distribution of ovulation by days of the cycle, counting from the onset of the last menstrual period, according to each of the three methods of dating. The frequency polygons are quite similar, the differences being insignificant in view of the relatively small number of cases. In this set of graphs and in Fig. 3, the four cases (Nos. 27 through 30) in which the greatest differences in the dating occurred are indicated by white blocks. Their distribution is such that they do not significantly modify the form of the frequency plots.

Fig. 3 gives the frequency distribution of ovulation by days of the cycle, plotted by summating the results of all three methods. This frequency polygon, which is probably the best estimate of the true distribution that can be constructed from the data of the thirty cases, because it averages out the discrepancies, agrees very closely with such information as we possess from pre-

vious investigations. The range is from day 8 to day 20, with the mode (peak of the curve, indicating the time at which ovulation most frequently occurs) at days 13-14.

It has been known for thirty years that in the human species ovulation takes place about the middle of the cycle. This knowledge has become more and more secure and has been put to practical use in the Knaus-Ogino method of control of conception, but precise observations on the distribution of ovulation, i.e., the modal date, the range in days from the earliest to the latest possible day of ovulation, and the form of the distribution curve, are still relatively limited.

In a report of very careful observations on 100 patients, Brewer and Jones (1947a) plot the frequency distribution of 54 ovulations in the same number of individuals, dated by calculating the day of ovulation from the estimated age of the corpus luteum at operation, and supplemented in some cases by study of the endometrium. The distribution was quite similar to that reported by us, the range being from day 8 to day 19, with the peak on day 14. The article of Brewer and Jones gives references, which need not be repeated here, to a number of studies of the time of ovulation by other, presumably less precise, methods, i.e., by study of body temperature fluctuations and of cyclic changes in the cervical mucus, and by timing the onset of excretion of pregnanediol glycuronidate from the corpus luteum. All these methods have indicated a similar pattern of ovulation frequency.

Very recently two other methods of ascertaining the time of ovulation, previously used in a limited way, have been applied more extensively. One of these is that of compiling cases in which conception resulted from a single insemination on a known day of the cycle. The date of effective insemination cannot in the present state of our knowledge be assumed to be the day of ovulation but they must be practically the same, for to the best of our knowledge neither ova nor sperm cells are long viable. Experience with the Carnegie rhesus colony shows that a mating to be effective must take place just before rupture of the follicle. Opportunities to collect cases of this sort have been rare, but the recent extensive use of the urinary rat test at The Wistar Institute has enabled Farris (1948) to present a graph of the distribution of ovulation as indicated by 50 human cases in which conception occurred when either coitus or artificial insemination was practiced on a specific day of the cycle. In this series the range of distribution of the day of effective insemination is day 8 to day 19, with the peak on day 11.

The study of vaginal smears provides still another method of determining the time of ovulation. Papanicolaou (1933) in a small series found a range from day 7 to day 17, with the mode at day 12. De Allende and Orías, who have acquired great proficiency in the study of the cycle by the Papanicolaou method, using Shorr's stain, have published a tabular summary (Cuadro III, p. 72 of their monograph of 1947) of 61 cycles in 28 women. The earliest ovulation occurred on day 11, the latest was on day 20, and the modal day was day 13.

An instructive study of the time of ovulation in another primate species is that of the rhesus monkey by Hartman, summarized in Fig. 68 of his *Time of Ovulation in Women,* 1936. In that species the enlargement and rupture of the ovarian follicle can be detected by palpation with a high degree of accuracy. In a series of observations much larger than our human series, the frequency distribution of ovulation was so nearly like that of our series that for practical purposes the same drawing could be used to depict them. The range of days on which ovulation occurs is the same, i.e. days 8 to 20, and the mode is on day 13, with high incidence also on days 12 and 14, as in our

series. It is indeed remarkable that our records, obtained in connection with extensive pathological conditions of the pelvic organs, match so closely those of Hartman from healthy and relatively young females of another species.

Returning to the human species, the total amount of data obtained by carefully controlled observations is (as we have said) not large, but the agreement with respect to the frequency distribution as observed by various methods is very striking. It seems unlikely that further work will significantly alter the picture we now have of the distribution of ovulation in the human cycle between days 8 and 20, with high frequencies from day 12 to day 15 and the mode at about day 13.

The congruence of our series with the others cited gives assurance of the significance of the evaluation thus afforded of the urinary rat test for ovulation. In view of this fact, the records of ovulation tests at The Wistar Institute now provide a much larger material for study of the time of ovulation than has been acquired by any other method. A portion of this material appears in a graph (Farris, 1948, Fig. 17) of the frequency distribution of 208 ovulations determined by the urinary rat test in 46 women whose fertility was proved by subsequent conception. In that series the earliest ovulation was slightly earlier than in our present series (day 6) and the range therefore slightly greater, i.e., day 6 to 20. The mode was on day 12.

The chief problems now before us as to the chronology of the human cycle involve the postovulatory phase, including such questions as the relation of early and late ovulation dates to varying cycle length, and the meaning of variations in the span between ovulation and the onset of the next menstrual period. For the study of these problems operative material is of no use because the cycles under study are interrupted by excision of the reproductive organs. Such observations as those here reported have served their purpose if they validate those tests, such as the urinary rat test, which can be applied without disturbance of the cycle.

Positive Test Wthout Ovulation; Late Regression of the Follicle.—In the six cases of group H of the foregoing protocols (Nos. 34 through 39), a positive test was obtained, indicative of ovulation on day 11 (2 cases), day 12 (3 cases), or day 14 (1 case); but subsequent study of the ovaries and endometria revealed no evidence of ovulation. It should be added that the ovulation tests, in four of the six cases, were considered to indicate abnormal reactions. These cases, occurring sporadically as the series was collected, were at first indeed puzzling, but it soon began to be evident that the aberrant cases had one factor in common, namely, the presence of a large ovarian follicle in abnormal condition, together with an endometrium in the mid- to late proliferative stage.

The histological state of the follicle was quite similar in each of these cases, varying chiefly in degree (Figs. 7 and 8). Although it was not possible to measure the size of the follicle in any of the six cases, because they were all collapsed, it is possible at least to say that the follicle was of a size approaching that at which ovulation takes place. The granulosa layer was composed of small cells with densely staining nuclei. Mitotic figures were absent. The granulosa cells did not show the morphological changes characteristic of the normal follicle in which ovulation is impending, i.e., a tendency to be drawn out into spindle shape pointing toward the lumen of the follicle, and a looseness of arrangement due to the presence of fluid between the cells. The theca interna showed in varying degrees a state which we have designated in the protocols as "luteinized"; that is to say, the theca was thicker than normal and made up of enlarged cells with much cytoplasm and vesicular nuclei, describable by the term "epithelioid." In several of the six cases the theca was much engorged with blood, both in the vessels and between the cells; but it is difficult to know to what extent this appearance was the result of trauma at operation.

This picture of relatively early retrogression of a large ovarian follicle varied in degree. In Case 34, for example, the pseudoluteinized state of the follicle wall, produced by loss of the granulosa and proliferation of the theca interna, must have been in progress for several days. In Case 38, on the other hand, the changes in both granulosa and theca interna were slight. Taken together, however, the six cases are very similar, and they indicate the existence of a special kind of ovarian crisis, characterized by the retrogression of a large follicle that has presumably developed normally up to a few days before ovulation should have taken place. The appearance of a gonadotrophic substance in the blood, which produces the test for ovulation, occurs in these cases as in normal cycles, giving indeed, in some of these cases indications of ovulation so precise that the ovarian and endometrial findings were quite unexpected.

The occurrence of anovulatory cycles of this special type, in six of the thirty-six cases giving positive urinary tests, is worthy of further attention. The existence of large follicles in early retrogression, often hemorrhagic, is known to gynecological pathologists, but their relation to the cycle has not been considered. If, as we think, this is a special form of follicular retrogression, it should be found by gynecological pathologists with special frequency in ovaries removed just about the usual time of ovulation in the cycle, i.e. day 11 to day 15. Our cases do not afford clues to the etiology of the condition. The six patients were all 35 years of age or older, and all but one had pelvic inflammatory disease, but in these respects they were as a group probably not significantly different from the other subjects of our study.

Summary

1. In thirty-nine women, the urinary rat test for ovulation was done, and the date of ovulation was estimated subsequently by histological examination of the ovaries and endometria obtained at operation. In twenty-six of the cases, the dating by the test, and by histological examination, agreed within one day or with a difference of only one day. In four cases there were differences of two, three, or four days. The frequency distribution of ovulation in the cycle resembled closely that found by various other methods of estimating the time of ovulation. Ovulation occurred between days 8 and 20 of the cycle, most frequently from days 11 to 14, with the peak on day 13. In three cases the test agreed with the evidence from the ovaries and endometrium that ovulation had not occurred.

These results show that the urinary rat test indicates the time of ovulation in a high proportion of cases with sufficient accuracy for clinical use, and that the frequency distribution of ovulation revealed by it in larger series of cases will be statistically valid.

2. In six cases there was a positive test in the absence of ovulation. In each of these cases one ovary contained a large follicle which had begun to retrogress shortly before the time at which ovulation would normally have occurred, characterized by changes in the granulosa ranging from cessation of mitotic activity to extensive breakdown, and by "luteinization" and sometimes vascular engorgement of the theca interna. This form of follicular atresia with onset just before ovulation presumably constitutes a pathological entity.

References

Brewer, J. I.: Am. J. Obst. & Gynec. **44**: 1048, 1942.
Brewer, J. I., and Jones, H. O.: Am. J. Obst. & Gynec. **53**: 637, 1947.
Brewer, J. I., and Jones, H. O.: Am. J. Obst. & Gynec. **54**: 561, 1947.
Brewer, J. I., and Jones, H. O.: Am. J. Obst. & Gynec. **55**: 18, 1948.
Corner, George W., Sr.: Carnegie Institution of Washington, Pub. 557, Contrib. Embryol. **31**: 117, 1945.
de Allende, Inés, and Orías, O.: La citología vaginal humana, Buenos Aires, 1947, Editorial *El Ateneo*.
Farris, E. J.: Am. J. Obst. & Gynec. **52**: 14, 1946.
Farris, E. J.: Anat. Rec. **95**: 337, 1946.
Farris, E. J.: Am. J. Obst. & Gynec. **56**: 347, 1948.
Farris, E. J.: The time of human ovulation. Motion picture film, Kodachrome, 16 mm., 400 feet, silent. 1948a.
Hartman, C. G.: Time of Ovulation in Women, Baltimore, 1936, Williams and Wilkins Company.
Hertig, A. T.: Diagnosing the endometrial biopsy, Proc. Conference on Diagnosis in Sterility, 1945.
Papanicolaou, G. N.: Am. J. Anat. **52** (supplement): 519, 1933.
Papanicolaou, G. N., Traut, H. F., and Marchetti, A.: The Epithelia of Woman's Reproductive Organs, New York, 1948, The Commonwealth Fund.
Rock, J.: Am. J. Surg. **48**: 228, 1940.
Schroeder, R.: Weibliche Genitalorgane (Normale Histologie). In: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, 1930, Julius Springer, vol. 7, pt. 1, pp. 329-556.

Wexler, D. J., Birnberg, C. H., and Kurzrok, Lawrence: Hysterogram in the Diagnosis of Uterine Bleeding, Am. J. Surg. **77**: 755, 1949.

The authors report a series of patients with abnormal uterine bleeding studied by means of a technique of hysterography which employs a nonoily radiopaque material. In no instance was an untoward effect noted from this method and a uterine abnormality was detected in approximately 75 per cent of cases. This evidence suggests the usefulness of such a technique in the gynecologic armamentarium.

These workers urge the use of such a method as a preliminary or substitute for curettage because it is their belief that diagnosis of the cause of uterine bleeding is "complicated," and curettage is "emotionally disturbing" to the patient for it requires hospitalization and an anesthetic. Furthermore, they state that diagnostic curettage may fail to reveal the cause of bleeding. Such inaccuracy of this simple gynecological examination has not been the experience of most workers in this field. It permits bimanual examination under anesthesia and also a frequent opportunity to carry out the desired therapy at the same time.

The case reports presented by the authors as evidence of the efficiency of hysterography are excellent illustrations of the necessity for eventual curettage or other operative therapy in the majority of these patients.

The authors properly condemn the administration of endocrine substances without first establishing a cause for abnormal uterine bleeding. S. B. Gusberg.

CONDITIONS OF BLOOD FLOW IN THE GRAVID UTERUS*

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THE causes of some of the complications of the last trimester of pregnancy are not known. This is especially true, despite much thought and speculation on the subject of pre-eclampsia, idiopathic premature labor, and missed abortion. The physiological conditions in the uterus which we are to discuss tonight may well bear on these conditions. Although I shall not give an explanation of these clinical problems, perhaps you will gain some insight into them which will render your role as obstetricians in the management of pregnancy a little less empirical—and a little more academic. We shall review the salient features of uterine blood flow during pregnancy.

Functions of Uterine Blood Flow

Uterine blood flow during pregnancy must provide for fetal nutrition and uterine growth. Both problems are of greatest importance to the obstetrician. He is of necessity obliged to deal with them. Fetal nutrition is necessary to assure on one hand a mature and viable baby, and on the other, uterine growth is necessary to assure that the powers of labor will be sufficient to effect delivery with least harm to the mother and her child. For both purposes, an ample supply of maternal blood must be available at all times. The physiologist who would understand the mechanisms of pregnancy must concern himself with them also.

To be correct, we should speak of the circulation of *bloods* in the uterus. The conditions of fetal circulation are quite different from those of the maternal circulation. Between the two circulations are the chorionic villous tissues and surfaces of more than two dozen cotyledons. These possess a great surface area for exchange of substances between the mother and fetus. Measurements by Christoffersen show that altogether the total area averages 14.6 square meters (minimum, 9.2; maximum, 20.6 square meters). Each cubic millimeter of fetal placenta contains some 33.6 square millimeters of surface. Special arrangements of the capillaries in the chorionic villi have been described which, it is postulated, yield an efficient mechanism for interchange of blood constituents between mother and fetus (Mossman, 1926; Barcroft and Barron, 1946).

In a functional sense, the maternal circulation is dichotomous. It provides nutrient materials for the uterus on one hand and for placental exchange on the other. The extent to which these two functions are dependent upon the arrangement of the uterine vasculature will be the principal topic discussed in this paper. First, however, I would like to discuss certain characteristics of the fetal circulation.

The Fetal Circulation

The principal features of the growth and function of the fetal circulation have been summarized recently (Reynolds, 1949) and so the subject need not be dealt with at length.

*Read before the Obstetrical Society of Boston, March 15, 1949.

Much is known concerning certain aspects of the fetal circulation while concerning others we are virtually in the dark. Barcroft reviewed many important facets of this subject in his last book, written, he said, as a kind of scientific last will and testament, and published in fact just before his death. From this book it is clear that much is known concerning the blood gases, hemoglobin, dissociation curves, and arterial and venous pressures in the fetus during intrauterine life. Barcroft aptly described the fetal vascular-respiratory relations as term approaches by the title of his Croonian Lecture, "Everest in Utero" (Barcroft, 1935). While he based his ideas on work of his own and that of his colleagues, it was Eastman who first stated that the response of the hematopoietic system of the fetus to the conditions of pregnancy near term is similar to that of the hematopoietic system to high altitude, and for the same reason, namely, oxygen lack resulting from insufficient mechanisms of exchange and transport (Eastman, 1930). To Barcroft, however, we are indebted for knowledge that critical respiratory conditions in the fetus at term are attributable in part to *diminished* maternal blood flow through the uterus and in part to an increasing disproportion between the sizes of the fetus and the placenta as term nears (see Reynolds, 1949).

One may safely predict that much more remains to be learned concerning the fetal circulation in the placenta. Preparations which Dr. Romney of the Boston Lying-In Hospital has obtained already suggest the nature of some of these discoveries. They are, in my judgment, very significant. While Romney's observations are morphological they promise to shed light upon the essential hemodynamics of fetal blood flow in the placenta and the mechanism of venous return to the fetus.

At present we are in the dark concerning the mechanism of venous return of blood from the placenta. There are no valves in the veins of the allantochorionic surface of the placenta, or in the umbilical cord (Spivack, 1946). Venous pressure is about 50 per cent of arterial blood pressure in the umbilical cord. This factor, along with that of the large diameter found in the cord vein, is calculated to assure movement of the blood through the cord (Barcroft, 1946). There is no benefit of gravity, no help from a thoracic pump, and there are no muscular movements to force venous blood toward the fetal heart such as one finds in the independent organism. These are the mechanisms that operate postnatally. Other mechanisms must account for the flow of blood from the placenta to the fetus.

When Dr. Romney visited the Carnegie Laboratory several months ago, he showed me injection corrosion preparations of blood vessels of the fetal placenta. One of the most striking features of these preparations is that, grossly to the eye, the caliber of the veins on the allantochorionic surface of the placenta is not much if any greater, generally speaking, than of the corresponding arteries. This shows that, by virtue of the nature of the circulation between the placenta and the fetus, the average linear velocity of blood flow in the veins is of the same order of magnitude as in the arteries. The pressure in these veins is known to be nearly half that in the arteries. It therefore seems reasonable (and preliminary calculations based upon measurements confirm) that the relative kinetic energy of blood flow in the umbilical veins approaches that in the arteries of the cord. It appears that we are on the threshold of appreciating for the first time the mechanism of venous return from the placenta to the fetal heart.

The means by which the problem of venous return from the placenta can be solved is exemplified by consideration of the conditions that obtain in the umbilical cord. The relative *linear velocities of blood flow* in the vessels of this structure can be evaluated in the following way:

The proposition may be postulated that:

(1) As much blood flows *to* the placenta from the fetus as returns except for that water which is picked up in the placenta and retained by the fetus for a given gain in weight within a unit of time, and

(2) The average linear velocity of blood flow in the veins compared to that in the arteries of the cord is a function of the relation between the cross-sectioned areas of the veins and arteries, respectively. There are two arteries and one vein. A picture of these vessels fixed in a distended position is shown in Fig. 1.

(3) It therefore follows that the *relative velocity* of blood flow in the vein compared to that in the arteries may be determined in the following way:

(a) The *volume flow* in the veins and arteries, respectively, is

$$V_v - \frac{W}{t} = V_{A_1} + V_{A_2} \tag{1}$$

or,

$$V_v = V_{A_1} + V_{A_2} + \frac{W}{t} \tag{2}$$

where V_v = c.c.s./minute blood flow in the vein; $\frac{W}{t}$ = gain in water/minute of the fetus; V_{A_1} and V_{A_2} = c.c.s./minute flow in each of two arteries in the umbilical cord. Since $A_1 = A_2$, therefore

$$V_v = 2\left(V_A + \frac{W}{2t}\right) \tag{3}$$

(b) The average linear velocity of flow in the arteries and veins may be expressed as follows:

$$\text{Velocity in the veins} = \frac{V_v}{\pi r_v^2 \cdot t} \tag{4}$$

and,

$$\text{Velocity in an artery} = \frac{\left(V_{A_1} + \frac{W}{2t}\right)}{\left(\pi r_{1,2}^2 \cdot t\right)} \tag{5}$$

where $r_{1,2}$ signifies the radius of either umbilical artery.

(c) The *relative* average linear velocity of flow in the umbilical vein compared to that in the umbilical arteries is obtained by relating equation (4) to (5) as follows:

$$\frac{\text{Linear Velocity in Veins}}{\text{Linear Velocity in Arteries}} = \frac{\left(\frac{V_v}{\pi r_v^2 \cdot t}\right)}{\frac{\left(V_{A_1} + \frac{W}{2t}\right)}{\left(\pi r_A^2 \cdot t\right)}} = \frac{V_v}{\pi r_v^2 \cdot t} \cdot \frac{\pi r_A^2 \cdot t}{V_A + \frac{W}{2t}} = \frac{2r_A^2}{r_v^2} \tag{6}$$

By simply measuring carefully, therefore, the radii of the umbilical arteries and veins respectively of normally distended vessels, one may determine the relative velocities of flow in these vessels.

In the case shown in Fig. 1, we find that the velocity of flow in the vein is 72 per cent of that in the arteries at the site of sectioning.

The conclusion that the average linear velocity of blood flow in the umbilical vein is nearly three-fourths that of the corresponding arteries has important implications. Their full import cannot be stated at this time. The most significant fact is that the large mass of venous blood is in relatively rapid motion resulting from the force of appreciable pressure.

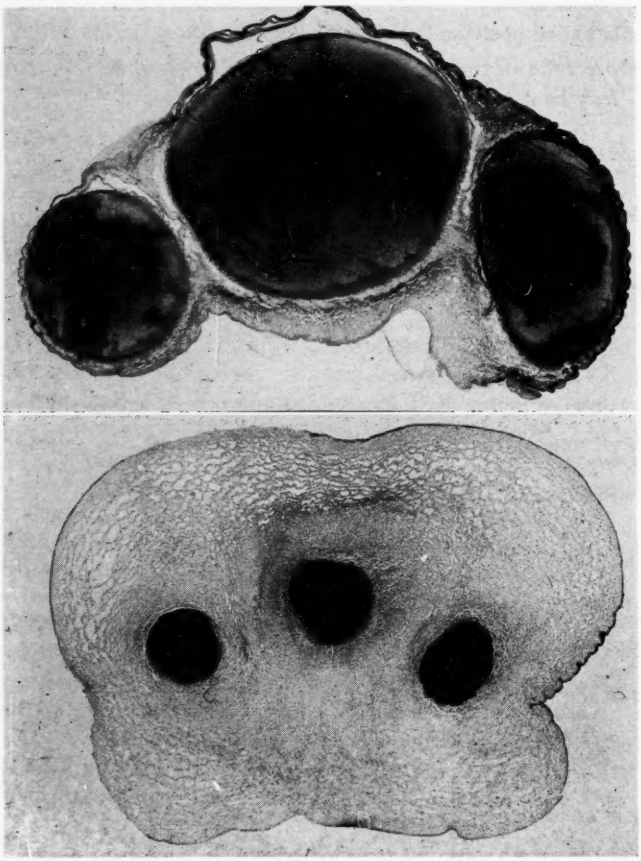

Fig. 1.—Cross sections of a human umbilical cord, approximately 20 cm. from the placenta. Top, section from a segment of cord which was clamped while the blood was still flowing, and fixed in the distended condition. This appears to be the first published picture of the state of the distended vessels. Bottom, section from an undistended region of the same cord. The latter is the conventional picture of cord sections. The former shows the relative diameters of the arteries and vein. The average linear velocity of flow is a function of these diameters. Calculations show that the flow in this vein is about 72 per cent of that in either of the arteries. (Same magnification.)

When this study has been applied to the arteries and veins of the placenta down to individual cotyledons, it will yield to us the first information available concerning the pattern of the hemodynamics of blood through the placenta. Even so, absolute values will be unobtainable and the approach is wholly that of the morphologist. Moreover, the work remains to be done. I thought you would find it interesting, however, to know that a solution to an old and unsolved problem may be realized. Its importance may lie in the fact that it should shed light on the cause of sudden fetal death at term.

The Maternal Circulation in the Uterus

I desire to call attention to observations made in the Carnegie Laboratory over the past three years. These are the subject of a paper which has been published (Reynolds, 1949). This study is concerned with three things: first,

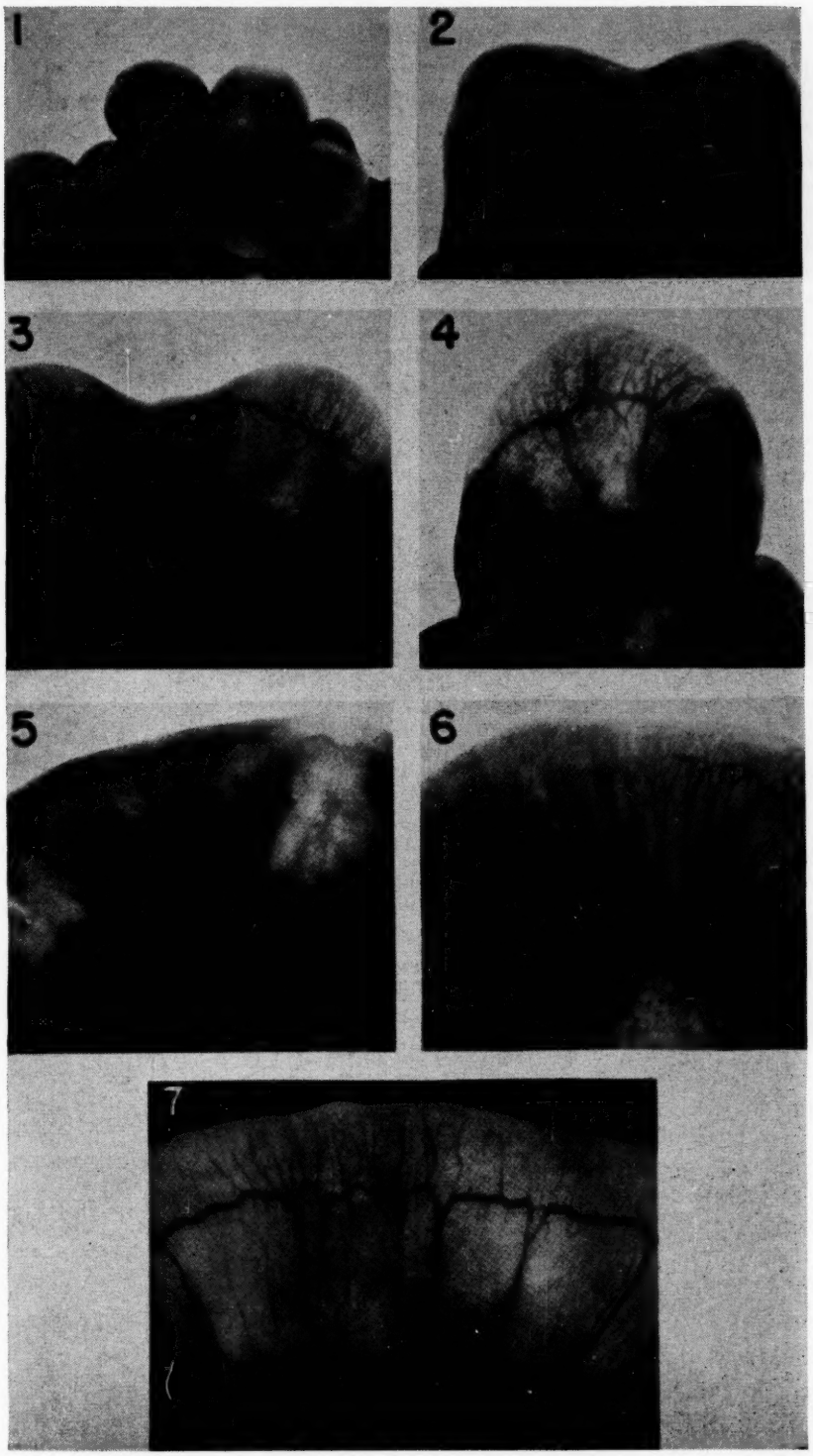

Fig. 2.—Conceptus sites in rabbit uteri injected with a diffusible dye (Prussian blue). (1) twelfth day of pregnancy; (2) sixteenth day; (3) twentieth day; (4) twenty-second day; (5) twenty-fourth day immediately after conversion of the conceptus to a cylindrical shape; (6) twenty-fourth day, later; (7) twenty-eighth day. Parturition on the thirty-second day. Note the increasing difficulty of injection of the blood vessels with the dye as the conceptus increases in size in the spherical shape but release of resistance to injection immediately after conversion. See text for description of hydrostatic basis of this.

the state of the minute vessels; second, the arrangement of the larger blood vessels in the uterus; and third, the flow of blood through them. The results of this study will be reviewed briefly.

(a) Patency of Minute Vessels Throughout Pregnancy.—Observations on the patency of the minute vessels of the rabbit uterus are shown in Fig. 2. These preparations were obtained by uniform injection of the uterus with a solution of Prussian blue. Precipitation of the dye occurs wherever the solution has penetrated into the tissues during the perfusion prior to excision of the uterus and placing it in acid.

It will be seen in Fig. 2 that on the twelfth and sixteenth days of pregnancy there is even distribution of the dye throughout the uterus. By the twentieth day, the tissues about the most distended portion of the uterus are devoid of dye, whereas other, nondistended regions of the uterus are richly injected. This is likewise true on the twenty-second day, as well.

When injections are made on the twenty-fourth day, however, one observes that the tissues are again easily injected with dye, and this continues up to the twenty-eighth day, just four days before parturition.

(b) Shape of Vessels and Patency of Vessels.—Your attention is called to the fact that prior to the twenty-fourth day, the shape of the uterus about a single conceptus is that of a sphere of increasing size. By the twenty-fourth day, the individual conceptus has become converted to a shape which is essentially cylindrical. This is associated, as one sees in Fig. 2, with improved patency of the minute vessels throughout the entire uterus.

These experiments show that the resistance to flow through the minute vessels of a dye solution injected into uteri under a constant head of pressure varies within different parts of the uterus at different times of pregnancy, *according to the shape and size of the conceptuses.* In the nongravid uterus, or in undistended portions of a gravid uterus, there is even and heavy distribution of the solution to all parts. There is also an even distribution of dye over the conceptuses, fully equal to that observed at interconceptus sites, until the sixteenth day (while the conceptuses are still spheroidal).

With continued growth of the conceptus, there is further stretching of the uterus. This growth is associated with decreased injection of the solution over the regions of maximum distention and a greater concentration of the dye in the interconceptus sites. This result shows that the attainment of maximum spheroidal size of the conceptus just prior to conversion serves to bring about stretching of the uterine tissues around the conceptus to such an extent that the minute blood vessels in this area are less patent than are those not so stretched.

By the mechanism of conversion from a spheroid to a cylinder in the latter part of pregnancy and with further growth of the conceptus restricted to growth in a longitudinal direction rather than in three dimensions, the patency of the minute blood vessels becomes restored so that the vessels may be injected with dye once again. This situation continues. despite extensive fetal growth, with little change until near the end of gestation.

(c) Rearrangement of Large Uterine Vessels Throughout Pregnancy.—The basis of the foregoing observation is to be found in the adjustments which the larger blood vessels of the uterus undergo during gestation. This is best shown in Fig. 3, which shows the arrangement of the veins about a conceptus on different days of pregnancy (twelfth, sixteenth, twentieth, twenty-fourth, and twenty-eighth).

In these, one sees that during the spherical phase of conceptus growth, the enlargement of the conceptus is limited to the region between two sets of circumferential veins. These pass around the uterus at each end of the implanted con-

ceptus. As the fetus, the fluids, and placenta grow, increasing tension is put upon the uterine vessels about the conceptus. Despite growth and increase in size of these blood vessels, there is resistance to flow of dye or plastic in them. This is demonstrated by failure of the antimesometrial uterine blood vessels to

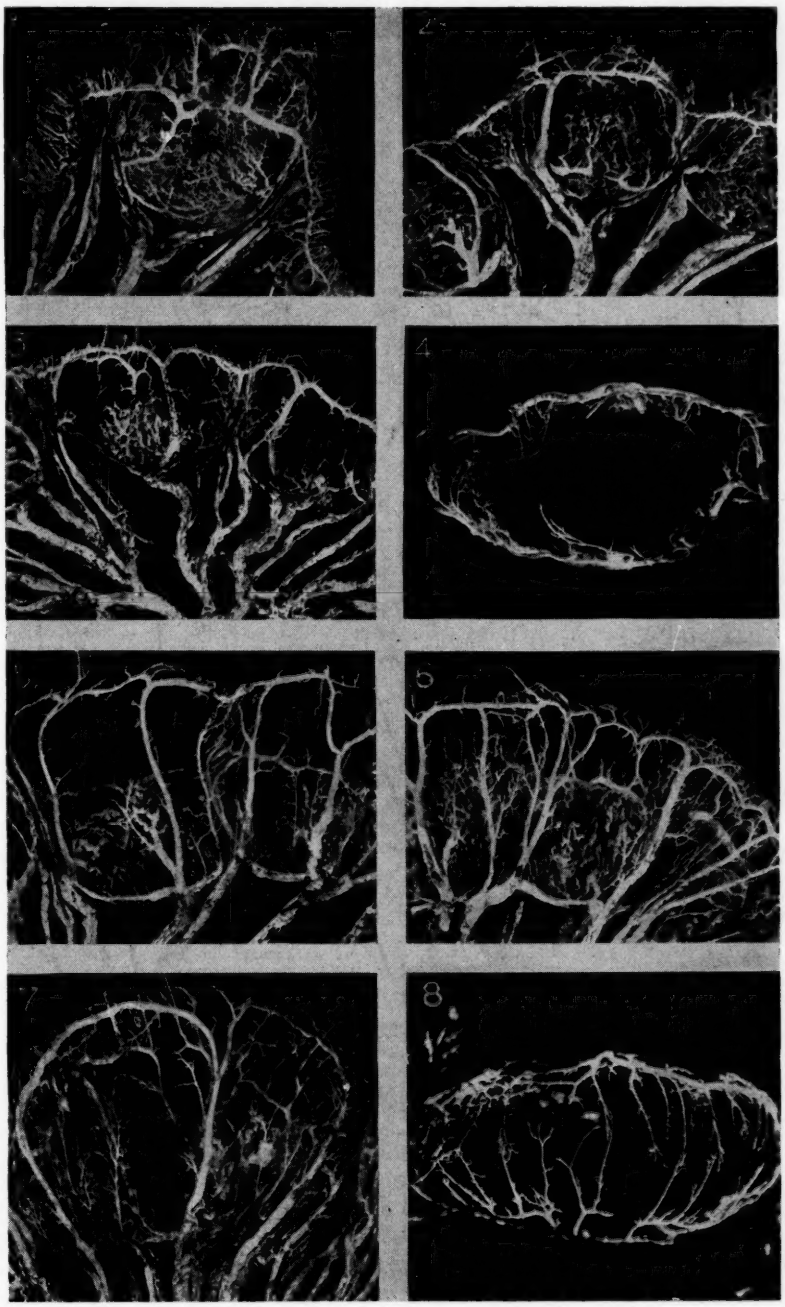

Fig. 3.—Vinylite casts of injected veins about conceptus sites on (1) twelfth day of pregnancy; (2) sixteenth day; (3) twentieth day, lateral view; (4) twentieth day, ventral view; (5) twenty-second day, just at the moment of conversion from sphere to cylinder; (6) twenty-second day immediately after conversion; (7) twenty-fourth day, lateral view; (8) twenty-fourth day, ventral view. Note the better injectability of the ventral vessels after conversion than immediately before, despite the much larger size of the fetus.

be injected on the twentieth and twenty-second days; after the conceptus changes shape, however, these same vessels are easily injectable, as may be seen in Fig. 3.

The foregoing results are summarized in Fig. 4. Here the patterns of changing morphological relations of two circumferential uterine veins and of three ventral collecting veins are shown for the nongravid uterus and for selected days of pregnancy.

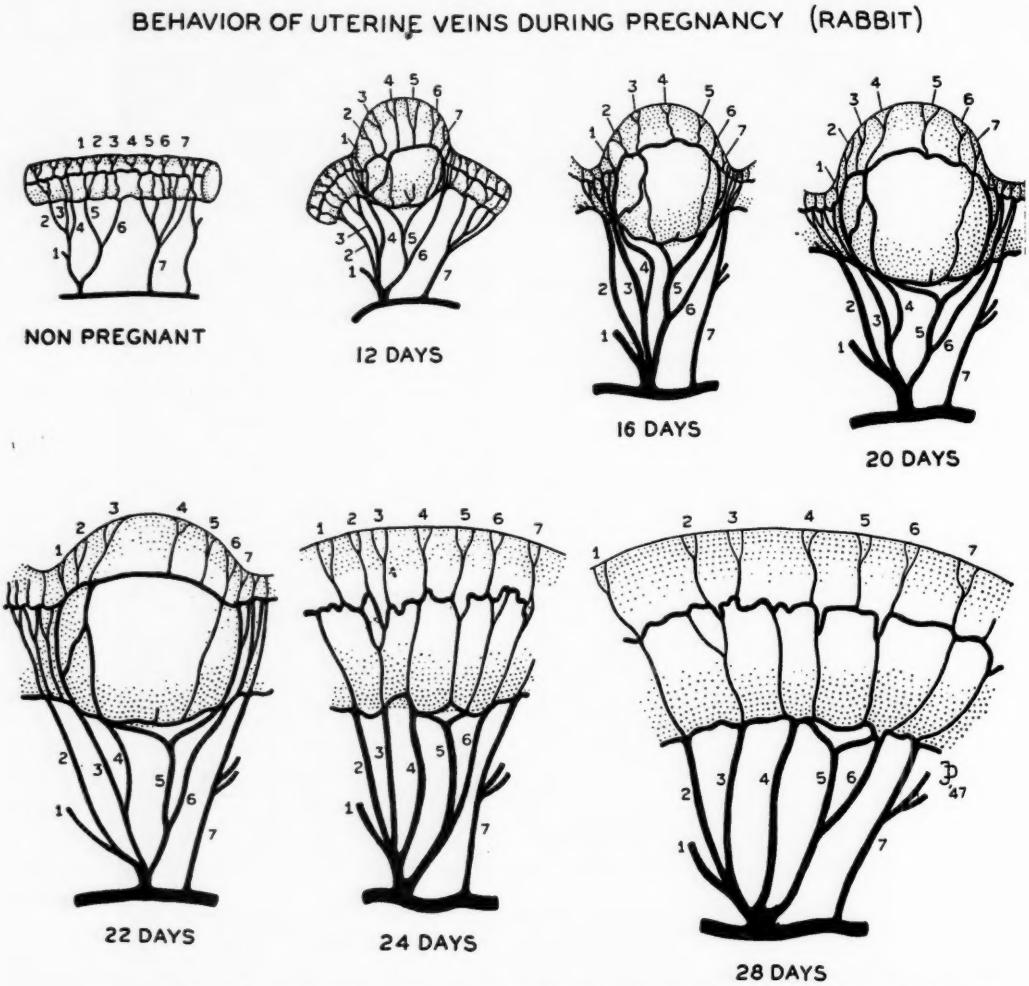

Fig. 4.—Schematic summary of the vascular rearrangement of the larger blood vessels about the rabbit conceptus before and after conversion of the uterus. Note effect of change of shape of conceptus on the distribution of the blood vessels along the lateral aspect of the uterus.

The basic venous pattern of the nongravid uterus is distorted by the spheroidal conceptus. The distortion involves separation of the two circumferential uterine veins at either end of the conceptus (with stretching of the tissues between them) and fanning out of the ventral collecting veins. As the conceptus reaches maximum spherical size, the separation of the veins reaches its most extreme degree.

The effect of conversion upon the arrangement of the veins is clear from the results which have been described. As a consequence of increased size of the spheroidal conceptus, a time is reached when the vessels, which until this

time have been increasingly crowded at the ends of the conceptus, take up positions along the lateral aspects of the conceptus. This change is accomplished in a short period of time, with the result that the veins over the entire conceptus are less stretched and more easily injected.

We see, therefore, that *the shape of the conceptus* determines the patency of the uterine blood vessels about this structure. This is true of the minute vessels as well as of the larger vessels around the conceptus. Obviously, the question arises, How are these observations related to the flow of blood around the conceptus?

(d) Maternal Uterine Blood Flow Around the Conceptus.—This is a subject which has been studied directly in rabbits. In this work, small amounts of sodium cyanide were injected directly into selected spots in the venous system of the uterus around a conceptus. Blood coming from anastomosing vessels swept the cyanide out of the uterus and into the systemic circulation. The moment of arrival of cyanide at the carotid body was determined by an inspiratory gasp. The circulation time is determined in the first place, therefore, by the rate of removal of cyanide from the uterus. The uterus-carotid body circulation times, plotted as circulation *rates* (i.e., $\frac{1}{\text{circ. time}}$) through the uterus are shown in Fig. 5.

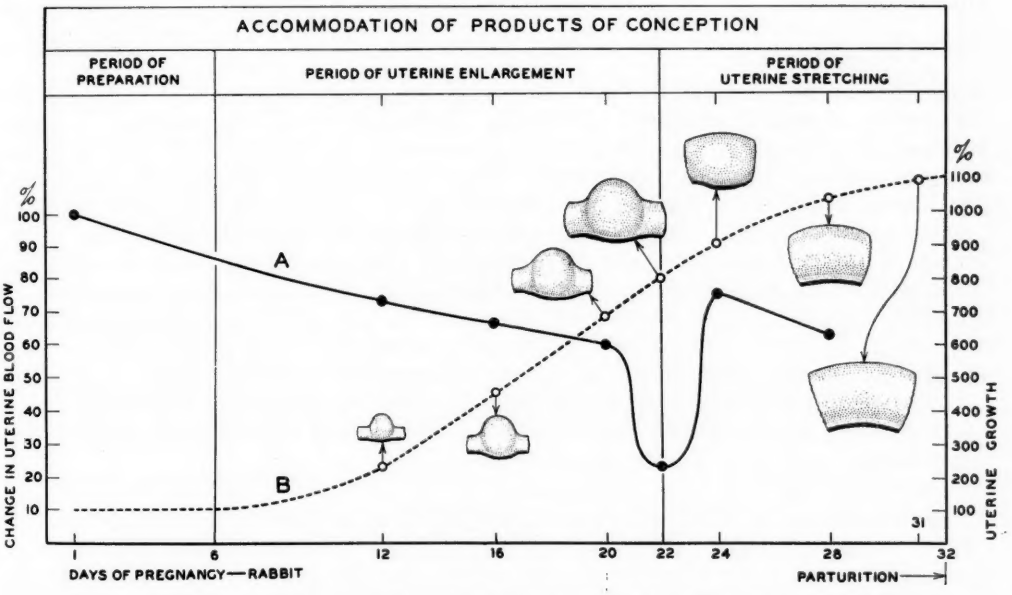

Fig. 5.—Curve of uterine growth (dotted line), conceptus size and shape (figures) and uterine blood flow through the blood vessels of the lateral uterine blood vessels. Correlate the uterine ischemia with the poor injectability of the blood vessels in Figs. 2 and 3.

The curve of blood flow in the lateral uterine vein about the region of greatest distention shows interesting characteristics. As the conceptus increases in size when it is spheroidal in shape, the rate of blood flow decreases progressively until the twentieth day of pregnancy. By the twenty-second day there is a profound decrease in the rate of blood flow. As the shape of the conceptus undergoes conversion from a sphere to a cylinder, there is prompt restoration of blood flow to levels which exist early in gestation when the fetus is very small. Once again, therefore, we observe that the shape of the conceptus critically affects the flow of maternal blood through the uterus.

What is the meaning of this intense but brief uterine ischemia? Without elaborating upon a point which has been described several times previously (Reynolds, 1946, 1947, 1948) this ischemia occurs because of changes in physical forces locally about the uterine vasculature. As the conceptus attains a maximum spheroidal size, tension within the tissues becomes maximal; with change of shape from a sphere to a cylinder, there is a sudden relief of tension. The physical, hydrostatic basis for this is discussed in the publications to which reference has just been made. The problem is fundamentally that of an elastic membrane subjected to varying tensions through which the blood is flowing. The uterus, stretched in one system of forces in equilibrium (i.e., sphere), reaches a limit of distention. It then suddenly comes to a new equilibrium under a different system of forces in a different shape (i.e., cylinder), and this is such that it favors restored circulation of maternal blood through the uterus.

Hydrostatic Factors Determining Local Blood Flow

The effect of shape of the conceptus upon the local flow of maternal blood suggests that there are different local rates of blood flow in the uterine tissues over the surface of the conceptus. That this is indeed so is shown by the following considerations:

Differential Tensions Within the Uterus.—The tension in any part of the distended uterus is a function of the local radius of the several curvatures. In the simplest case, that of a round balloon, the tension is a geometric function of the radius ($T = \frac{r^2 \cdot p}{2}$). An attempt to assess this in the pregnant rabbit uterus was made by measurement of the dimensions of pregnant uteri and handling the data with equations suited to spheroids. Measurement of the radii of 273 conceptuses in 47 rabbits made it possible to evaluate the areas of high and low tensions in different parts of the uterus. Thus the amount of tension on the side of the uterus relative to that on the mesometrial or antimesometrial aspect of the uterus was evaluated. These are, in effect, differential tensions (Reynolds, 1949). In spheroids this is determined by raising the radii to the third power and comparing them to each other. Thus the tension in the tissues on the side of the uterus compared to the tension in the tissue on the antimesometrial surface of the uterus is in proportion to the diameter along the mesometrial axis, cubed, divided by the diameter, cubed, of lateral axis through the conceptus.

In spheroids, the tension on the lateral aspect of the uterus is determined by the following relationships (where a and b are the appropriate semiaxes; p, the intrauterine pressure; T_1, the lateral tension):

$$T_1 = \frac{\left(\frac{a^2}{b}\right) \cdot p}{2} \tag{7}$$

The tension on the mesometrial surface or the antimesometrial surface ($T_{m\text{-}a}$) is as follows:

$$T_{m\text{-}a} = \frac{\left(\frac{b^2}{a}\right) \cdot p}{2} \tag{8}$$

When the relation of $T_1 : T_{m\text{-}a}$ is determined, the equations just cited clear algebraically to

$$T_1 : T_{m\text{-}a} :: a^3 : b^3 \tag{9}$$

In other words, the semiaxes (i.e., the two radii) raised to the third power and compared to each other will yield the relative (i.e., the differential) tensions between the lateral and the mesometrial or the antimesometrial aspects of the uterus. For cylinders, the relation is in the following proportion:

$$T_l : T_{m\text{-}a} :: a^2 : b^2 \qquad (10)$$

Fig. 6 shows the result of application of these facts to the rabbit conceptus during pregnancy. Briefly, this chart shows that, as the spheroidal conceptus becomes larger and larger, the tension on the lateral aspects of the uterus becomes twice as great as that in the mesometrial or antimesometrial aspects of the uterus. After the sphere is converted to a cylinder, the differential in tension between these areas becomes much less marked.

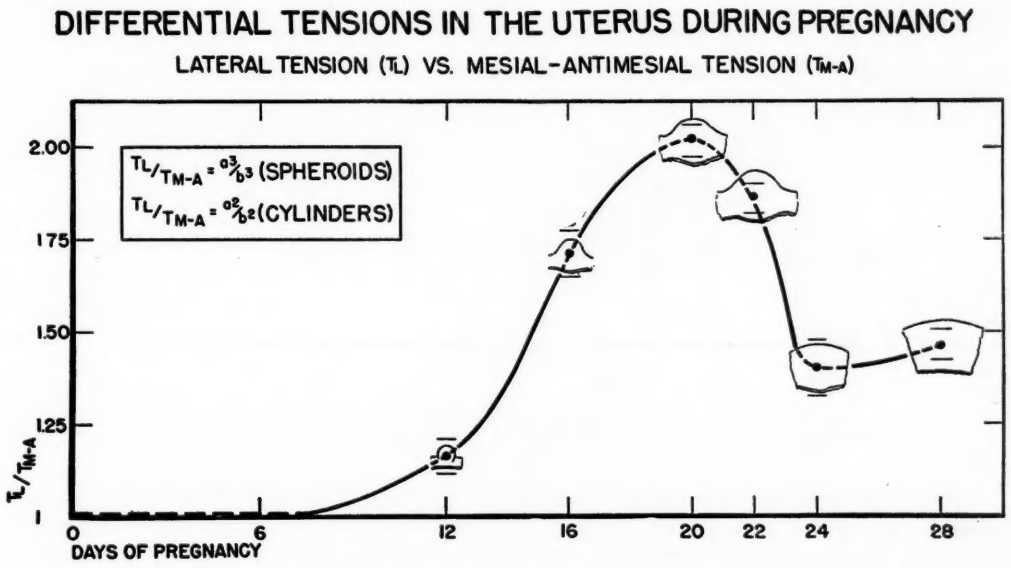

Fig. 6.—Graph of the relative difference in tensions between the lateral tissues in the uterus and the ventral aspects of the uterus. Note that the tension in the lateral tissues of the uterus increases progressively until the twentieth day of pregnancy. After conversion to a cylinder, the tensions in the tissues become more nearly equalized.

We see, therefore, that the local shape of any part of the surface of the uterus covering a conceptus, being a function of the local radius of curvature, governs the local tissue tension within the uterus. Of what import is this to the local flow of maternal blood throughout the uterus? It has a twofold importance.

In the first place, Fig. 7 shows the relation of uterine blood flow to the differential tensions just discussed. Here it will be seen that, as the tension in the lateral part of the uterus increases relative to that in the mesometrial-antimesometrial axis, the rate of uterine blood flow in the lateral uterine vein diminishes, irrespective of whether the conceptus is spheroidal or cylindrical. Clearly, therefore, the local radius of curvature determines the local blood flow through the wall of the uterus. In the second place, local tissue tension in the uterus determines that there shall be a favored placental circulation for the reasons discussed below.

A Favored Placental Circulation.—How is the placental circulation influenced by local tissue tension? The answer to this relates to what happens to the

placental circulation at the time of uterine ischemia when the spheroidal conceptuses change to a cylindrical shape. To appreciate this we must understand the character of the uterine vasculature.

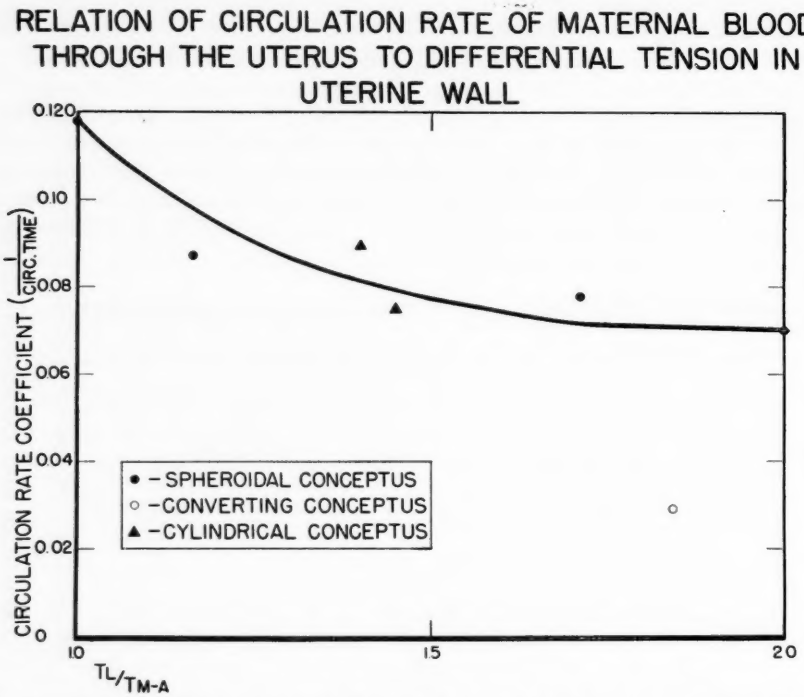

Fig. 7.—Graph showing that, as the tension in the lateral uterine tissues increases, the blood flow progressively diminishes. Thus local tissue tension exerts an influence on local blood flow.

The pattern of the uterine circulation in the rabbit is a dual one. As the arteries enter the mesometrial aspect of the uterus, they divide. One group of branches passes circumferentially around the uterine wall providing it with an arterial supply; the other passes to the mesometrial folds of the endometrium to which the placenta becomes primarily attached. The result of this arrangement is that when the circulation of blood in the uterine wall is decreased as its radius of curvature (and tension) increases, blood, which would ordinarily flow through those channels, will be deflected necessarily into the path of least resistance. This is into the placenta. It follows, accordingly, that the placental circulation is increasingly favored with respect to the rest of the uterus when it becomes ischemic prior to conversion. These changes are shown schematically in Fig. 8. The diagrams are drawn to scale with radii of curvature proportional to those obtained by measurement of actual conceptuses.

We are thus brought to the conclusion that hydrostatic factors within the uterine tissues affect the local flow of maternal blood through the blood vessels within them, and that these factors have an important bearing upon the welfare of the fetus. The pattern of hormonal changes within the maternal organism throughout pregnancy contribute at any given time to these hydrostatic conditions by altering uterine metabolism and tone. These hormonal changes act, however, in conjunction with morphological, geometric, and hydrostatic conditions to achieve the effects outlined above.

Another important feature of the results which have been described is found in the pattern of vascular changes observed during the period of uterine stretching. This is the time of most active fetal and least uterine growth. One might

suspect that this would be the period of greatest stretching of the uterine blood vessels. Such is not the case. The physiological data on maternal blood flow, on dye injection, and on injection of plastic all show that the blood vessels remain patent. This is because they pass around the uterus circumferentially, and that as the fetus grows it does so by merely moving these vessels apart from each other without substantially increasing their length. We see, accordingly, that no increased energy is necessary for pumping blood through these vessels although there is a very great increase in the size of the uterine contents. This result is achieved solely by virtue of the cylindrical shape of the uterus and the relation of the circumferential vessels to it during the period of uterine stretching.

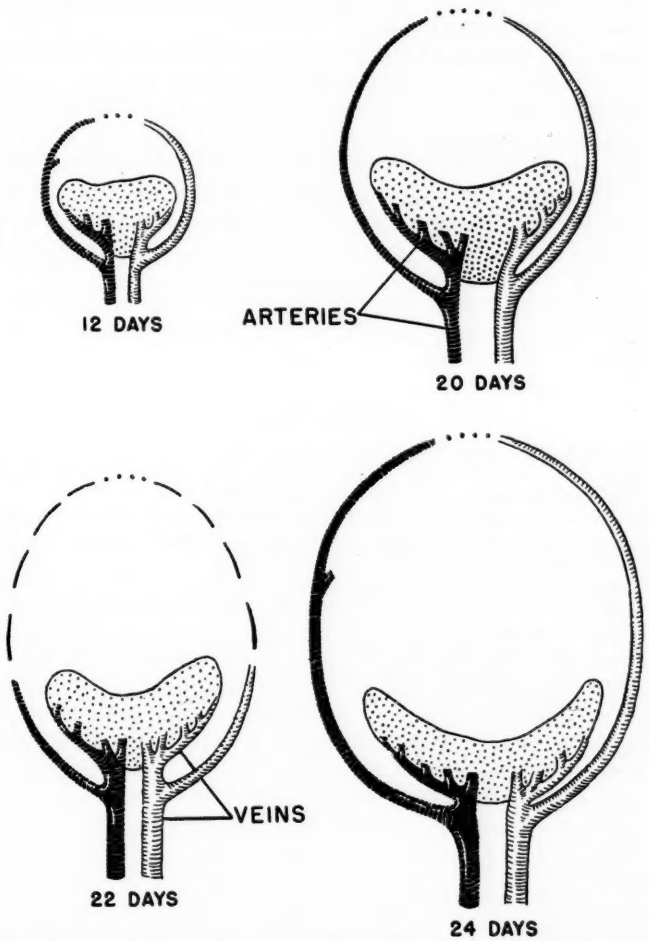

Fig. 8.—Schematic diagram showing the relations of the blood vessels to the uterine wall and to the placenta in the rabbit (cross sections) on different days of pregnancy. As a result of an increasing lateral radius of curvature, tension is built up in these tissues. This interferes with the flow of blood through the uterus, and deflects it into the placenta. So at the time of uterine ischemia, prior to conversion of the conceptus from a sphere to a cylinder, there is a favored uterine circulation.

Uterine Accommodation in the Uterus Simplex

As obstetricians, you will ask, Do these conclusions apply to the uterus simplex? The final answer to this cannot be stated now. Observations on the uterus of Macacus rhesus show that a pattern of growth and change of shape of the conceptus occurs which is exactly comparable to that seen in the rabbit.

The duration of gestation in this species is about 160 days. Conversion from an ovoid to a cylindrical shape occurs abruptly between the 100th and 105th day (Gillespie, Ramsey and Reynolds, 1949). Experiments now in progress are designed to measure the uterine circulation rate with the uterus and abdomen both intact. (Gillespie and Reynolds, 1949.)

Finally, a study of the growth and shape of the human uterus is now in progress by my associate, Dr. E. C. Gillespie. We already know that there are two critical periods in which abrupt changes of shape take place. The first of these occurs between the twentieth and twenty-second week, at which time the lower uterine segment begins to be incorporated into the body of the uterus. The second occurs at about the twenty-eighth to the thirtieth week. It involves a change in the growth pattern of the body of the uterus itself in ways which are being revealed by continued study.

In conclusion, we return to the theme at the outset of this paper. We were confronted with the fact that certain complications of late pregnancy have in common one feature, namely, their tendency to occur most frequently at the beginning of the last trimester of pregnancy. From what we have seen concerning uterine growth, fetal growth, uterine shape, and uterine blood flow. it is clear that there inevitably are vascular crises within the uterus. Ordinarily, the shape of the uterus is such that the necessary change in shape of the uterus takes place without jeopardizing the requirements of continued fetal growth. This depends upon the maintenance of a favorable shape of the uterus at all times. If it should be that such conditions are not maintained, placental ischemia would take place in a manner and to a degree which may affect adversely the course of gestation.

References

Barcroft, J.: Proc. Roy. Soc. London, s.B. **118**: 242, 1935.
Barcroft, J.: Researches on Pre-Natal Life, Oxford, 1946, Blackwell Scientific Publications.
Barcroft, J., and Barron, D. H.: Anat. Rec. **94**: 569, 1946.
Christoffersen, K.: Om Villusoverfladens Dimensioner i den Fuldbaarne Placenta: en quantitativt histologisk studie. Thesis, Copenhagen, 1936, Levin and Munksgaard.
Eastman, N. J.: Bull. Johns Hopkins Hosp. **47**: 221, 1930.
Gillespie, E. C., Ramsey, H., and Reynolds, S. R. M.: Am. J. Obst. & Gynec. **58**: 758, 1949.
Gillespie, E. C., and Reynolds, S. R. M.: Proc. Soc. Exper. Biol. & Med. **70**: 721, 1949.
Mossman, H. W.: Am. J. Anat. **37**: 433, 1926.
Reynolds, S. R. M.: Anat. Rec. **95**: 283, 1946.
Reynolds, S. R. M.: Am. J. Obst. & Gynec. **53**: 901, 1947.
Reynolds, S. R. M.: Carnegie Inst. of Washington Publication 583, Contrib. Embryol. **33**: 1, 1949.
Reynolds, S. R. M.: Physiology of the Uterus, ed. 2, New York, 1949, Paul B. Hoeber, Inc.
Spivack, M.: Am. J. Obst. & Gynec. **52**: 387, 1946.

Rh ANTIBODY STIMULATION WITH AN Rh-NEGATIVE FETUS (Rh ANAMNESTIC REACTION) AND ITS SIGNIFICANCE TO THE NEWBORN

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THE present report is based upon three anamnestic* reactions for the Rh factor,† found among 6,185 women delivered at Woman's Hospital between Jan. 1, 1947, and July 1, 1948.

The course of antibody production resembled that associated with pregnacies having Rh incompatibilities.

Despite the high antibody levels in maternal and newborn sera, evidence of hemolytic disease was absent.

These cases are of more than usual interest not only because of their diagnostic implications, but also for the bearing they have on our understanding of the mechanism of the Rh immunization.

Report of Cases

CASE 1.—(W.H. C-82368.) A 23-year-old unmarried white woman was first seen in the clinic at Woman's Hospital during the fifth month of her third pregnancy. Her only illnesses, other than childhood diseases, had been hemorrhagic complications incidental to her two previous pregnancies, treated both times by transfusions. There had been no abortions and no allergies.

After her first delivery, unattended, at term in April, 1942, she had been taken to a city hospital for treatment of hemorrhagic shock and for the repair of a laceration which had extended into the rectum. Her postnatal course was uneventful except for a "reaction with shaking chills" following the second of two transfusions; the first of type O, the second from her mother was type A. There was no record of Rh typing of the bloods.

The baby weighed 3,470 grams and was normal. The baby's twelve-day record was not suggestive of erythroblastosis.

The second pregnancy was by a different father three years later. In the staff service of a second hospital in December, 1945, after delivery of the placenta, there occurred "profuse uterine bleeding" with a "loss of 500-600 c.c. of blood." A transfusion of type A was discontinued after administration of "about 100 c.c." of blood because of a chill which lasted "eight minutes" and a fever of 40° C. (The patient stated that a technician informed her that this blood was subsequently found to be "Rh positive.") Urinalysis dated the following day was normal. On her first postpartum day another transfusion, recorded by the laboratory as "type O, rh negative," was uneventful. Presumably the typing was for D.

This second baby weighed, 3,940 grams. He developed a moderate icterus thirty-six hours after birth. The pediatrician diagnosed "erythroblastosis, mild." Capillary smears showed "immature erythrocytes, polychromasia, anisocytosis, and poikilocytosis." The

*The anamnestic reaction is defined as a renewed production of an antibody without renewed exposure to the specific antigen.

†The term Rh standing by itself indicates the entire family of Rh-Hr types. For clarity, the Fisher and Race[15] notations C, D, E for the types Rh′, Rh$_0$, and Rh″, and c. d, e for the types of Hr′, Hr$_0$, and Hr″ will be used in this report.

baby's blood was "type A, Rh positive." His hemoglobin was 13 grams per cent on the sixth day, gradually falling to 10 grams at two weeks and to 8 grams with an erythrocyte count of 2,400,000 per cubic millimeter at 36 days. Transfusions, each 90 c.c. of "type O, rh negative" blood were given on days 39 and 40. At three weeks he had been "removed from breast feeding." He was discharged on the forty-first day.

According to follow-up reports, the first two children at ages 6 years and 3 years were healthy and mentally normal.

The course of the third pregnancy, at Woman's Hospital, was uneventful. The father was different from either of the fathers of the previous children. In May, 1948, four days before the calculated date of confinement, because of apprehension arising from the behavior of the Rh antibody levels, medical induction was begun.

Because of her history of postpartum hemorrhages, laboratory studies had been carried out to exclude hemorrhagic dyscrasias. The results were within normal limits. Cross-matched blood, available for transfusion, proved not to be needed at delivery. There was only moderate retroplacental blood loss. The puerperium was uneventful. This absence of correlation with bleeding in this anamnestic case (and for the two cases below) is in agreement with the general conclusion[13] that there is no correlation between Rh sensitizations and uterine hemorrhage.

This third baby cried spontaneously. She weighed 4,100 grams. The baby was not edematous either in a generalized manner or in the local regions of the eyelids or of the tongue. Neither the liver nor the spleen was palpably enlarged. The pediatrician found the baby to be so normal that she deferred transfusion despite the behavior of the maternal Rh antibody. The hemoglobin was 22 grams per cent on the first and second days of life. Premature erythrocytes were absent from the capillary smears; the leucocyte count was 18,000 per cubic millimeter. Icterus did not develop at any time. The baby enjoyed normal development up to the present age of six months.

The blood types for this third pregnancy are shown in Table I. It was concluded that this baby was truly rh negative. This is in contrast to those children who appear to be rh negative when tested at birth but later prove to be Rh positive.[4, 6, 9, 12] In such falsely rh-negative babies, the Rh-positive erythrocytes are coated with incomplete or "blocking antibodies" and hence may fail to agglutinate when tested with the standard saline typing sera.[19, 20, 21] That this baby was truly rh negative was determined by repeated typing with C, D, and E sera, both in the saline and in the albumin method, at 3 days, 2 weeks, 5 weeks, and at 3 months of age.

TABLE I. BLOOD TYPES AND GENOTYPES OF ERYTHROCYTES AS DETERMINED BY AGGLUTINATION WITH KNOWN ANTI-SERA

	BLOOD TYPE								
			RH-HR						PRESUMPTIVE
	ABO	MN	C	D	E	c	d	e	GENOTYPE
Case 1.—									
Mother	A_1	MN	–	–	–	+		+	cde/cde
Father	A_1	M	+	+	–	+		+	CDe/cde
Baby girl	A_1	M	–	–	–	+		+	cde/cde
Case 2.—									
Mrs. B. M.	O		+	–	–	+			Cde/cde
Mr. W. M.	O		+	+	–	+			CDe/cde
Baby boy M.	O		–	–	–	+			cde/cde
Case 3.—									
Mrs. R. J.	O		–	–	–	+		+	cde/cde
Mr. C. J.	A		+	+	–	+		+	CDe/cdE
Baby boy J.	O		–	–	+	+		+	cdE/cde
Sister J. J.	O		+	+	–	+		+	CDe/cde

When the father's erythrocytes were available, one month after the baby was born, they were agglutinated by the mother's serum. The baby's cells were not.

The maternal antibody titers were measured from the seventh month of pregnancy until six months post partum as shown in Fig. 1. The laboratory determined the titers against CDe and against cDE cells and recorded the highest value. The first order[5] or saline antibody test was negative at all times. The second order[5] or albumin antibody was found in the sera of mother and child in the temporal relationships shown in Fig. 1. The blocking antibody titer was determined at six months post partum only; its titer was then 128, one-fourth of the total albumin antibody titer of 512 (Fig. 1).

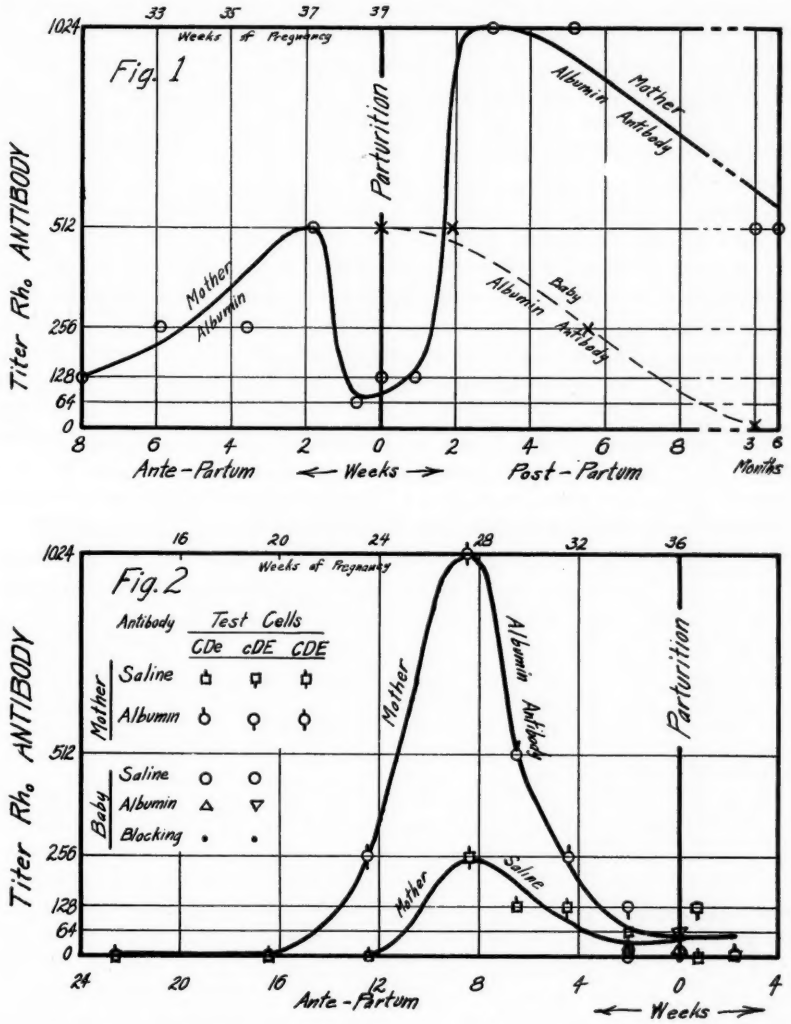

Fig. 1.—Course of antibody titers of Case 1.
Fig. 2.—Course of antibody titers of Case 2.

Concerning the initial maternal titer (Fig. 1), it is to be recalled that appreciable levels of antibody may persist for some months or years after a sensitization to Rh positive erythrocytes.[6, 7, 13, 16, 21] Hence the first measured titer, 128, in this pregnancy may have been carried over from the previous pregnancy in all or in part. It is noteworthy that the postpartum residual which followed the mere anamnestic response of this pregnancy, although decreased at six months to a titer of 512, was still four times as high as the initial level.

CASE 2.—(W.H. C-70493.) Mrs. B. M., a 23-year-old white woman, was followed closely during her third pregnancy in 1947 because of a history of erythroblastosis. Her case, a referred one, is summarized briefly elsewhere.[21]

In her past history, tuberculosis had been suspected but not proved; she had progressed through her two previous pregnancies without adverse sequelae. Her history was negative for abortions, transfusions, and allergies.

From her first pregnancy, delivered elsewhere at term in 1943, she obtained a normal, living boy of 3,700 grams. He has developed normally at five years.

The second child, weighing 3,900 grams, was delivered at term in 1945 at another hospital. He had a normoblastosis of 500 per 100 leucocytes with a leucocyte count of 11,000 per cubic millimeter. He developed jaundice and an anemia of 2,800,000 erythrocytes per cubic millimeter. He died at 2 days of age, despite transfusion with rh-negative blood. At autopsy he was found to have hepato- and splenomegaly with areas of erythropoiesis, pulmonary and gastric hemorrhages, and necrosis of the right lobe of the liver. The pathologic diagnosis was "erythroblastosis fetalis."

In this pregnancy, her third, the course of her serum antibody titers was as shown in Fig. 2. Because of the similarity of this course to those leading to severe erythroblastosis fetalis[3, 6, 11] she was delivered prematurely at Woman's Hospital, June, 1947, by cesarean section, at 36 weeks, and sterilized by tubal ligation. The puerperium was uneventful.

The baby was a normal, premature boy weighing 2,600 grams. There was no clinical evidence of erythroblastosis fetalis. The baby cried spontaneously and at birth there was no evidence of respiratory distress. At age 2 hours, however, continuous oxygen was started because of a "dusky color" and "much mucus." In the incubator, his color improved but the respirations were rapid and grunting and the mucus was still troublesome. At five hours, he still became dusky if the oxygen were discontinued; his temperature was 38° C. His condition became progressively worse, without development of jaundice, anemia, or splenomegaly and death followed gasping respirations at the age of 53 hours.

The nucleated erythrocytes in the peripheral blood varied from 1 to 2 to as many as 10 to 15 per 100 leucocytes, with the leucocyte count varying from 16,000 to 20,000 per cubic millimeter. Concurrent hemoglobin levels were 19, 17, 18, 15, 17 grams per cent during the fifty-three hours of life.

At autopsy there was no edema or jaundice; neither the liver nor the spleen was enlarged. Microscopically there was no evidence of extramedullary hematopoiesis or of hemosiderosis. The pathologic diagnosis was "prematurity, atelectasis and bronchopneumonia" with "no evidence of erythroblastosis."

The blood types of this family are shown in Table I (Case 2). The mother's serum agglutinated the father's erythrocytes, but not the baby's. The Rh type of the baby's cells was critically tested in the following ways: The cells were not agglutinated in the saline or in the albumin methods using anti-C, -D, -E or -c test sera. Nor were the erythrocytes from the cord blood agglutinated in the anti-human globulin test of Coombs,[2] thus demonstrating that these were not Rh-positive cells that had become coated with Rh blocking antibody[5, 19, 20, 21] (or for that matter, not cells that had become coated with any other antibody). The elution test which also detects possible antibodies coating the erythrocytes[5, 14, 21] was negative against both CDe and cDE cells.

Serum from the baby's cord blood contained albumin antibody of a titer of 64 when tested against CDe cells, and of 8 against cDE cells (Fig. 2). Assays for saline and for blocking antibodies were negative.

Maternal Rh antibodies were detected from the seventh week of pregnancy, onward. The saline antibody increased markedly, the albumin antibody even more markedly, both rising to a maximum early in pregnancy—28 weeks. Blocking antibody was present at a low titer at the initial visit at seven weeks; presumably it was not present during the last trimester because the saline antibody was readily measured then. Unfortunately, the patient moved early in the puerperium and it was not determined whether there was a renewed antibody production post partum as in Cases 1 and 3.

CASE 3.—(W. H. C-72733.) Mrs. R. J., a 28-year-old white housewife was electively delivered of her third pregnancy at 36 weeks by cesarean section in 1947.

There were no abortions or transfusions. She has had "hay fever" since the age of eleven, and at fifteen months post partum she was receiving weekly injections for "asthma" which had troubled her for the past six months.

Her first baby, an Rh-positive girl (Table I, Case 3) born in 1941, was normal in the neonatal period and has developed normally at seven years except for "hay fever" of four years' duration.

Her second baby, a boy, was stillborn at Woman's Hospital in 1946, three days after the heart sounds failed; the 39-week fetus of 3,600 grams was macerated and edematous but not icteric. The placenta weighed 1,100 grams; the capillaries of its villi contained numerous nucleated erythrocytes and there were islands of hematopoiesis among the villi. The liver, spleen, and lungs had foci of erythropoiesis. The pathologic diagnosis was "erythroblastosis fetalis."

During this pregnancy, her third, because of an increasing antibody titer (see below) approval for cesarean section was given at consultation and the pregnancy was terminated at 37 weeks "in order to prevent a recurrence of the hydrops" in August, 1947, at Woman's Hospital. The puerperium was uneventful. A normal, premature boy of 3,100 grams was obtained.

The pediatrician found no signs of erythroblastosis although these had been anticipated. There were no nucleated erythrocytes; the leucocyte count was 15,200 per cubic millimeter. The hemoglobin was 14, 20, 17, 15, and 15 grams per cent until discharge in the care of the mother on the sixth day. Tests for neonatal serum antibodies had not been performed. The baby has developed normally at the age of fifteen months.

The blood types of this family are given in Table I (Case 3). That the baby was truly cdE/cde was confirmed by re-typing at fifteen months; the mother's serum then agglutinated the father's, but not the baby's, erythrocytes.

The maternal antibody titers had been followed from the twenty-eighth week of pregnancy until delivery. Saline antibodies were not found. The albumin antibody increased from a titer of 2, at the twenty-eighth and thirty-second weeks, to a titer of 64 at the thirty-sixth week; it was 32 at the time of cesarean section at the thirty-seventh week. Unfortunately, no postpartum titers were then measured.

However, antibody levels at fifteen months, measured for the purpose of this study (with no intervening pregnancy) were markedly increased, suggesting that a postpartum stimulation of antibody production had occurred, not unlike that of Case 1. Saline antibodies were doubtfully present at a titer slightly greater than one; albumin antibodies were present to a titer of 128 against both CDe and cDE cells. Blocking antibodies were present to a titer of 4 against CDe cells and of 2 against cDE cells.

D Specificity of the Antibodies

Saline and albumin antibodies: In Table II are shown the types of cells against which the sera of the three cases were tested. In each case it can be seen that anti-D must have been present.

TABLE II. ANTIBODY SPECIFICITY OF SERA, AS DETERMINED BY AGGLUTINATION OF KNOWN ERYTHROCYTES

	TEST CELLS						THEREFORE ANTIBODY SPECIFICITY
	CDE	CDe	cDE	Cde	cdE	cde	
Case 1.—							
Mother		+	+	–	–	–	Anti-D
Baby Girl		+	+	–	–	–	
Case 2.—							
Mrs. B. M.	+	+	+			–	Anti-D*
Case 3.—							
Mrs. R. J.	+	+	+	–	–	–	Anti-D

*See text.

In Cases 1 and 3, at the times that the last of these tests were completed, six and fifteen months post partum, respectively, the antibody must have been exclusively anti-D since the sera agglutinated cells with the D antigen and only those with the D antigen.

Since the serum of Case 2 did not agglutinate cde cells it could not have contained anti-c, -d, or -e. That the mother was C positive herself, excluded anti-C. It cannot be excluded that she may have developed anti-E, also, although this is one of the less frequently formed antibodies.

Thus, in each case there was an Rh anamnestic reaction of D specificity, and apparently of this specificity only.

Blocking antibody: Freshly obtained six months and fifteen months post partum, sera of Cases 1 and 3, respectively (Case 2, not available), were used as sources of blocking antibody. The sera were diluted 50 per cent with saline suspensions of known CDe cells and of known cDE cells. After incubation for one hour at 37° C., aliquots of each series were tested for agglutination by known saline agglutinating sera of specificities C, D, and E. In these tests the anti-D serum, and the anti-D only, was blocked by the sera of these mothers. The blocking antibody was therefore of D specificity, and apparently of D specificity only.

TABLE III. BLOCKING ANTIBODY SPECIFICITY OF SERA, AS DETERMINED BY BLOCKING OF AGGLUTINATION OF KNOWN ERYTHROCYTES BY KNOWN ANTI-SERA

	TEST CELLS				
	CDe		cDE		
	TEST ANTI-SERUM		TEST ANTI-SERUM		THEREFORE BLOCKING SPECIFICITY
	C	D	D	E	
Case 1.— Mother	+	–	–	+	Anti-D
Case 3.— Mrs. R. J.	+	–	–	+	Anti-D

Summary of Cases

Three Rh anamnestic cases of late pregnancy were studied. These were of D specificity: D antibodies were produced in d/d mothers carrying d/d fetuses. Due to incomplete sampling it is not excluded that additional cases of this kind, or perhaps of other Rh-Hr specificity, may have occurred without detection. During the same interval there were sixteen cases of erythroblastosis fetalis, diagnosed clinically or at autopsy.

Two of the three pregnancies involved were in frequent Rh groupings: these were CDe/cdE in Case 2, and Cde/cde in Case 3. There were no ABO incompatibilities between mother and baby in any of the three cases.

In each case the anamnestic reaction was observed in the third pregnancy. Each father was D positive, of necessity D/d. Only one mother had a history of transfusions; these had coincided with the terminations of her previous pregnancies. In no case was there a history of abortion. In one case there was a history of allergy.

That there had been previous maternal sensitization was substantiated in each case by hospital records of erythroblastosis fetalis in the second-born child.

The course of the maternal Rh antibody levels was similar in each case, and not unlike that of a single case reported elsewhere.[3] Blocking antibody titers, as such were determined on a few occasions only, third order or cryptagglutinoid[5] titers not at all. First order or saline antibodies, and second order or albumin antibodies were followed. In each case there was a profound increase in maternal albumin antibodies and in one case, of saline antibodies, during the

latter half of pregnancy. The antibody titer again decreased prior to term to lower but still appreciable levels. In the two cases that were still available for measurement, the titer again increased after delivery, remaining for several months post partum, at a level markedly higher than on the initial determination during pregnancy.

In each case the baby was free of signs of erythroblastosis fetalis. Unfortunately, the hemoglobin levels were not followed throughout the neonatal periods so that the possibility of anemia could not be excluded. However, in none of the cases could sensitivity of the fetal erythrocytes to the maternal serum be established by laboratory means, although every attempt was made to do so.

It cannot be excluded that there may have been an incompatibility of some of the possible Rh subgroups such as are currently being reported, or of blood groups or tissue factors which may be discovered later. However, regardless of the possibility of such extraneous incompatibilities the observed reactions of these three cases fulfill the conditions of benign anamnestic reactions since in each case the specific D antigen was lacking during this pregnancy.

In each case the pregnancy had been terminated electively, the proximate indication being elevation of Rh antibody levels. The resultant babies, however, were no more susceptible to the antibodies than were their mothers. One baby died, not of erythroblastosis, but of complications attendant upon the elective termination of pregnancy.

Discussion

The contention that prenatal antibody production is indicative of an Rh-positive fetus[7, 8, 9] can no longer be entertained in view of the intense anamnestic reactions reported here and by others elsewhere.[3, 12, 13, 14]

Fetal Prognosis.—

That maternal Rh antibodies do not necessarily indicate clinical erythroblastosis, even in an incompatible pregnancy, has been shown repeatedly.[1, 3, 5, 6, 9] More significantly, the extensive data of several investigators[3, 6, 7, 12, 13, 14] does indicate that a prolonged elevation of maternal Rh antibody correlates with poor prognosis for the Rh-positive fetus.

By contrast to these conservative generalizations, it has been positively stated that increasing mortality of the fetus correlates with rapidly increasing titer of maternal antibodies, and that a precipitous decrease of titer is indicative of death in utero.[3, 7, 8] Taken as a single criterion, the course of antibody production in each case studied above would have pointed toward hemolytic diseases of the fetus, either on the basis of these statements or on the basis of the more conservative interpretations above. Indeed, the antibody course and the additional assumption that the fetus was Rh positive provided the basis for termination of the pregnancy in each case. The outcome in each case provides an example that antibody production alone is not an adequate basis for interference.

Incidence of Rh Anamnestic Reactions.—

Among the statistical series of the Rh reactions of pregnancy, there is a predictable weighting with matings to the "dangerous" homozygously positive fathers[14] (for discussion see also accompanying report[17]). There is a resultant relative paucity of rh-negative babies among the already sensitized mothers. Nevertheless, even so low an incidence as one benign anamnestic reaction among every six Rh antibody reactions of pregnancy is significant in practice.

Therapy.—

Several prophylactic or therapeutic measures have been tried either post partum or ante partum. Among these are: competitive specific sensitization,[18] antihistamine therapy,[8] Rh hapten therapy,[11] exchange transfusion,[19] long

spacing of pregnancies,[10] premature termination of the pregnancy,[13, 14] artificial insemination with rh-negative spermatozoa,[14] therapeutic abortion, and sterilization. An immediate indication for initiating one or more of these treatments, as in the cases reported here, has often been an increasing maternal antibody level. Such forms of therapy as may ultimately be proved beneficial must be weighed for a balance of benefits against the risks, to mother and to child, inherent in the treatment itself.

Despite spacing of pregnancies, in the above cases as much as two years apart, enormous antibody production was observed and this even in the absence of specific stimulation.

Early termination of the incompatible pregnancy is of doubtful benefit to the baby[13, 14] because of the morbidity and mortality which is consequent to the induced prematurity, or to the method of delivery, or both. The death of the unaffected baby of Case 2 serves only to emphasize the dangers of early termination of pregnancy, irrespective of Rh status.

Increasing maternal antibody levels may be interpreted as a warning signal for antenatal preparation for exchange transfusion[19] or for supplemental transfusion of the newborn. Yet the above cases emphasize the necessity of demonstrating neonatal sensitization also, and this preferrably on *cord blood.* Such demonstration may perhaps be satisfactorily performed with the albumin test method, or with Wheeler's glue test,[21] but the Coombs' test[2] is particularly to be recommended because its range of sensitivity is so wide as to include any erythrocyte sensitization. Such detection not only directs attention toward sensitized babies but spares those with benign anamnestic reactions from major procedures, which, for them, are unnecessary.

Prenatal control of antibody levels with Rh hapten[11] may yet provide the most effective and safest prophylaxis and therapy.

Summary

1. The Rh anamnestic reaction was studied in three rh-negative mothers. Each had become previously sensitized to the D factor. High anti-D titers developed in d/d mothers although this time carrying d/d fetuses.

2. Because the course of antibody levels resembles that of incompatible pregnancies, it is concluded that it is not possible to distinguish, by means of the antibody behavior alone, between a benign anamnestic reaction and one which may lead to erythroblastosis.

3. In each of the three cases studied, pregnancy had been electively terminated because of concern for the fetus. The three babies were without signs of erythroblastosis fetalis, although one infant died from respiratory complications incidental to the intervention.

4. It is concluded that obstetric or pediatric intervention based on maternal Rh antibody production *alone* is not well advised. Intervention may serve only to expose mother or child or both to such risks as are inherent in the interventions themselves.

This opportunity is taken to express appreciation to Miss Daphne Carnochan for special assays in this work.

References

1. Carter, B. B.: Am. J. Obst. & Gynec. 54: 879, 1947.
2. Coombs, R. A., Mourant, A. E., and Race, R. R.: Brit. J. Exper. Path. 26: 255, 1945.
3. Davidsohn, I.: Blood, Special Issue No. 2: 139, 1948.
4. Donohue, W. L., and Fremes, I. A.: J. Lab. & Clin. Med. 33: 526, 1948.

5. Hill, J. M., Haberman, S., and Jones, F.: Blood, Special Issue No. 2: 80, 1948.
6. Howard, J., Lucia, S. P., Hunt, M. L., and McIvor, B. C.: AM. J. OBST. & GYNEC. **53**: 569, 1947.
7. Kariher, D. H.: Virginia M. Monthly **73**: 347, 1946.
8. Kariher, D. H.: AM. J. OBST. & GYNEC. **54**: 1, 1947.
9. Kariher, D. H., and Miller, D. I.: Am. J. M. Sc. **212**: 327, 1946.
10. Levine, P.: J. A. M. A. **128**: 946, 1945.
11. Loughrey, J., and Carter, B. B.: AM. J. OBST. & GYNEC. **55**: 1051, 1948.
12. Page, E. W., Hunt, M., and Lucia, S. P.: AM. J. OBST. & GYNEC. **52**: 794, 1946.
13. Philpott, N. W., Latour, J. P. A., and van Dorsser, G. J. E.: AM. J. OBST. & GYNEC. **52**: 926, 1946.
14. Potter, E. L.: Rh: Its Relation to Congenital Hemolytic Disease and to Intragroup Transfusion Reactions, Chicago, 1947, The Year Book Publishers, Inc.
15. Race, R. R.: Blood, Special Issue No. 2: 27, 1948.
16. Sacks, M. S., Kuhns, W. J., and Jahn, E. F.: AM. J. OBST. & GYNEC. **54**: 400, 1947.
17. Schneider, C. L.: AM. J. OBST. & GYNEC. **59**: 371, 1950.
18. Wiener, A. S.: Proc. Soc. Exper. Biol. & Med. **58**: 133, 1945.
19. Wiener, A. S., and Wexler, I. B.: Blood **4**: 1, 1949.
20. Witebsky, E., Rubin, M. I., Engasser, L. M., and Blum, L.: J. Lab. & Clin. Med. **32**: 1339, 1947.
21. Zuelzer, W. W., Wheeler, W. E., and Leonard, M. F.: Pediatrics **1**: 799, 1948.

Philpott, Newell W.: The Use of Methionine in Obstetrics, Surg., Gynec. & Obst. **88**: 794, 1949.

Dr. Philpott discusses the rationale of the administration of methionine to patients with hepatorenal syndrome, hypoproteinism, and other conditions leading to widespread liver and kidney damage.

Methionine is, experimentally at least, lipotropic. In animals, in spite of low protein intake, the administration of this substance prevents fatty infiltration of the liver even in the presence of toxic agents. Methionine was given to pregnant women suffering from severe pre-eclampsia and eclampsia. Improvement was manifested by estimation of liver function, chiefly by means of the cephalin-cholesterol test. There was also clinical improvement as evidenced by an increase in the urinary output and a diminution in the edema. Methionine and choline were given to pregnant women with acute infectious jaundice. These drugs had no influence on the course of the disease. However, it was hoped that the subsequent cirrhotic changes might be minimized or prevented. The number of cases treated was too few for analysis.

Methionine was also given to women with isoimmunization, in the hope that it would cross the placenta and prevent excessive liver damage in their unborn infants. Liver function tests carried out on the infants after birth showed far less damage when methionine was used. Fetal survival rate was also much improved.

The author feels that the results have been promising but not conclusive.

LOUIS M. HELLMAN.

THE INCIDENCE OF URETERAL OBSTRUCTION IN BENIGN AND MALIGNANT GYNECOLOGIC LESIONS*

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IT HAS been known for over a century that ureteral dilatation and hydronephrosis might accompany pregnancy, complete prolapse of the uterus, and pelvic malignancy; but it was not until the advent of intravenous urography that the frequent occurrence of ureteral obstruction in conjunction with such lesions as ovarian cysts, fibromyoma of the uterus, and pelvic inflammatory disease became known.

During the past decade various clinical and radiographic studies have suggested that the ureter is involved so frequently that urologic study is essential to the proper understanding and correct management of many patients with extensive gynecologic lesions.

Study of the urinary tract by intravenous urography in patients with extensive gynecologic lesions has been a routine procedure on the ward service at the Jefferson Medical College Hospital for the past five years.

This study is based upon a review of the case histories and radiographic studies† of 379 patients admitted to the Division of Gynecology, Department of Obstetrics and Gynecology of the Jefferson Medical College Hospital from Oct. 1, 1943, to Nov. 1, 1948.

Our purpose is simply to determine the frequency with which ureteral obstruction has been encountered in a group of patients with extensive pelvic disease, and to compare our findings with the observations of others.

Ovarian Neoplasms

The incidence of urinary tract obstruction in cases of ovarian cysts was found to be 40 per cent by Everett and Sturgis[1] in a study of five cases, and 81.8 per cent by Kretschmer and Kanter[2] in a study of eleven cases. In a previous study the senior author[3] found compression of the ureters in three of four patients with large ovarian cysts.

In addition to mechanical factors which cause ureteral obstruction in large ovarian tumors or infiltrating malignant growths, there may be an added physiologic factor in the case of the feminizing mesenchymomas.

The larger cystic tumors frequently mold themselves into the pelvis and may compress the ureters at the pelvic brim. The site of compression is probably influenced by the size, consistency, and shape of the tumor. The obstruction usually occurs on the side on which the tumor originates; however, this is not always true as is illustrated by the following report:

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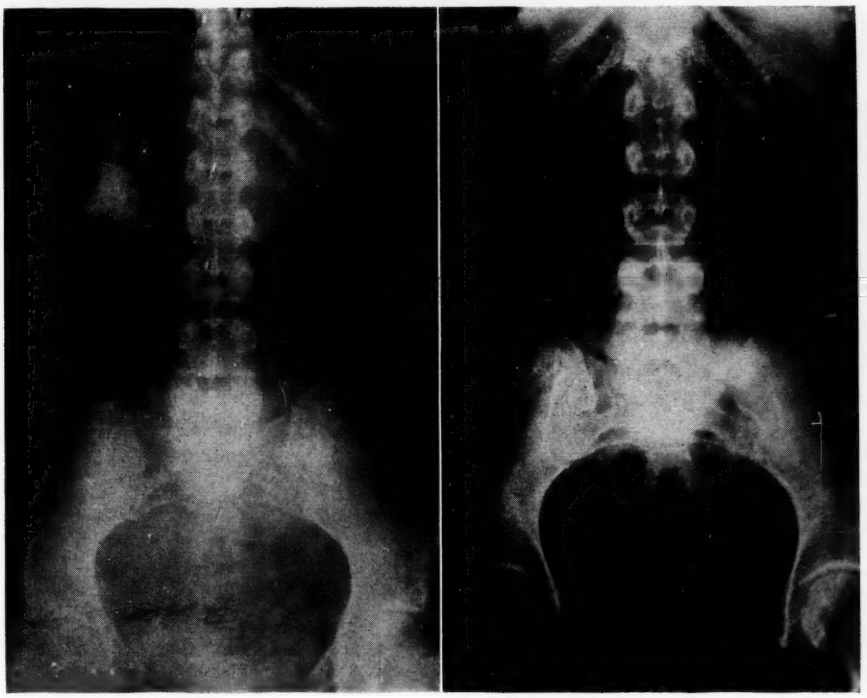
†The authors wish to express their appreciation to Dr. Lewis C. Scheffey, Professor of Obstetrics and Gynecology and Head of the Department of Obstetrics and Gynecology, and to Dr. Paul C. Swenson, Professor of Radiology in the Jefferson Medical College, for the opportunity of making this study.

Miss M. R., aged 23 years, was admitted to the Jefferson Hospital Nov. 22, 1946, with the complaint of intermittent pain in the right lumbar region which radiated anteriorly down the right side of the abdomen into the right thigh for the past year. There had been no change in her menstrual cycles. Urinalysis and urine concentration tests were within normal limits. An intravenous urogram on Nov. 23, 1946, revealed no excretion from the left kidney and slight stasis of the right urinary tract. A serous cystadenoma of the right ovary which extended to the costal margins was removed on Nov. 25, 1946. Re-examination of the urinary tract eleven days later by intravenous urography disclosed prompt function from both kidneys (Fig. 1).



A. *B.*

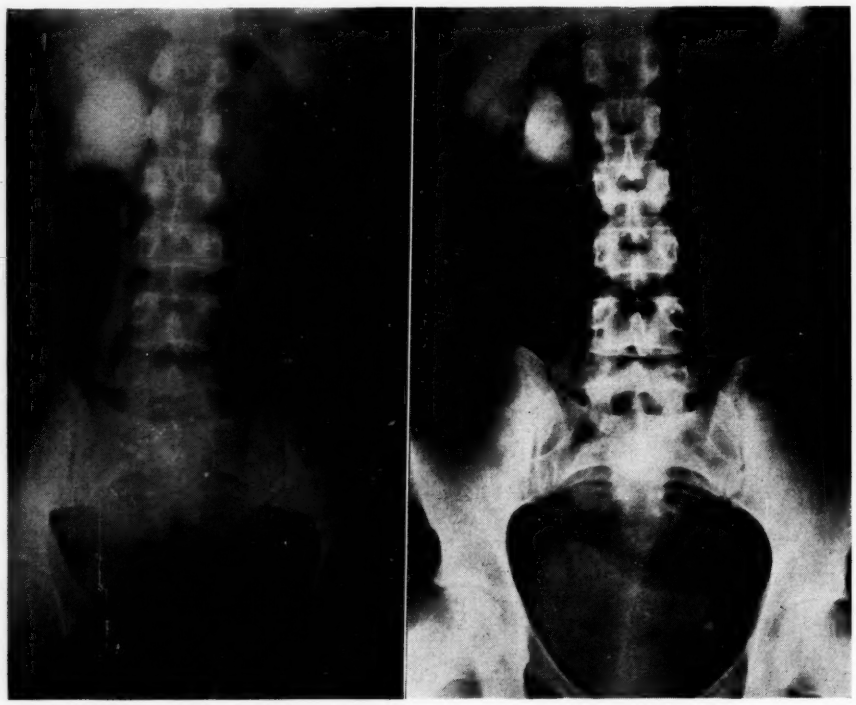
Fig. 1.—*A*, Intravenous urogram before operation showed no excretion from left kidney, and slight steasis of right urinary tract. *B*, Re-examination eleven days after operation showed prompt function of both kidneys.

In the feminizing tumors there must be considered the effect of hormones upon the ureter which would give rise to similar changes, noted by many investigators, in the urinary tract during pregnancy. One patient with a granulosa-cell tumor was studied before operation:

Mrs. M. W., aged 36 years, was admitted to the Gynecological Ward of the Jefferson Hospital on Oct. 14, 1947, with complaint of irregular menstrual periods and feeling of fullness in the pelvis. After the birth of her last child in 1937 her periods recurred only once a year. Hormone assays obtained the day of admission revealed 12 mouse units of urinary estrogen for twenty-four hours, and less than 6 mouse units of urinary gonadotropins in twenty-four hours. An intravenous urogram made on Oct. 16, 1947, revealed a nonfunctioning left kidney and right hydronephrosis and hydroureter. On Oct. 17, the patient showed signs of internal hemorrhage. At operation by Dr. Charles Lintgen the abdominal cavity was filled with blood and a solid right ovarian tumor about 7 cm. in diameter was seen to be ruptured and bleeding actively from several areas. Histologic examination disclosed a granulosa-cell tumor. Urinary hormone assays taken on the eighth postoperative day revealed 44 mouse

units of estrogen and less than 6 mouse units of gonadotropins. Four weeks after operation the left kidney was still functionless, but the right hydroureter and hydronephrosis had almost completely disappeared (Fig. 2).

In view of the fact that the size and location of the tumor did not seem to be sufficient to cause compression of the ureter, we believe the changes in the right urinary tract may have been due to hormonal influence. The absence of function from the left kidney is probably an unrelated finding.



A. *B.*

Fig. 2.—*A*, Intravenous urogram prior to operation showed nonfunctioning left kidney, and right hydronephrosis and hydroureter. *B*, Re-examination thirty-two days after operation showed left kidney still functionless, but right hydronephrosis and hydroureter almost completely disappeared.

Although the estrogen level was low, long-continued hormone stimulation may have caused changes in the ureters similar to the findings during pregnancy. Hofbauer,[4] also Hundley[5] and his associates, have noted hyperplastic changes in the musculature and in the connective tissue of the pelvic portion of the ureter during pregnancy. This had caused narrowing of the lumen of the ureter which is further accentuated by the engorgement of the vessels and edema of the tissue in the area. These changes were attributable to hormonal influences.

We have studied 32 patients (Table I) with ovarian tumors which were, with one exception, larger than a four months' pregnant uterus. There was

TABLE I. INCIDENCE OF URINARY TRACT OBSTRUCTION ASSOCIATED WITH OVARIAN NEOPLASMS

OVARIAN TUMORS	BILATERAL	UNILATERAL		NONE	TOTAL
		RIGHT	LEFT		
Benign	5	5	1	8	19
Malignant	6	3	0	4	13
Total	11	8	1	12	32

involvement of the urinary tract in 11 of 19 cases (57.8 per cent) of benign ovarian tumors, and in 9 of 13 cases (69.2 per cent) of malignant ovarian tumors.

Carcinoma of the Uterine Cervix

Howard Kelly[6] stated that probably the most common cause of bilateral hydronephrosis in women is cancer of the uterine cervix. Mansur[7] has found ureteral damage to be a far more serious and frequent complication of irradiation therapy of cervical carcinoma than damage to bowel and bladder.

The underlying cause for the frequent urinary tract obstruction has been studied by various investigators, each of whom has concluded that one or more of the following factors are responsible: ureteral blockage due to pressure of tumor tissue from without; infiltration of the ureteral wall and sheath by carcinomatous tissue by direct extension; metastasis to the ureter by way of the perivascular lymphatics; ureteral obstruction due to transient edema or inflammation of the tissues in the bases of the broad ligaments; and ureteral obstruction due to postirradiation fibrosis.

Drexler and Howes[8] found the cause of blockage of ureters in their series, in almost every patient, to be due to broad ligament extension of the malignant process. They state the incidence today is no more than before the advent of x-ray and radium therapy.

Graves, Kickham, and Nathanson[9] noted that the obstruction in the ureter was usually found 4 to 6 cm. above the ureteral orifice where the ureter lies close to the cervix. This finding has been confirmed by Howes and Strauss.[10] If vaginal extension has occurred the ureter may be involved at a lower level because of the proximity of the distal end of the ureter to the anterior vaginal wall.

Graves, Kickham, and Nathanson demonstrated carcinomatous tissue in the walls of the ureters causing either a narrowing or complete obstruction of the ureter.

Carson[11] reports finding a metastatic tumor mass in the ureter 15 cm. below the uretero-pelvic junction. The tumor cells in this case were found in the perivascular lymphatics of the ureter. He also mentions a report of thirteen similar cases by Garceau in 1909.

According to Schmitz,[12] transient edema of the tissues in the bases of the broad ligaments, cellulitis, and pelvic infection may result from the application of radium.

Tissue changes incident to irradiation effect occur very promptly but infection incident to radium application is not manifest usually for several days.

Martin and Rogers[13, 14] showed that filtered radiation up to 2.5 erythema doses produced no serious changes in the ureter of a dog within six weeks. Their later experiments, however, indicated that 75 mg. hr. of radium from needles inserted along the ureter in the dog are well beyond the safe limit and might lead to death with obstruction of both ureters. A dose of 54.3 mg. hr. applied in the same manner produced only partial stricture formation.

There are an ever-increasing number of reports of urinary tract obstruction resulting from contracting scar tissue in the parametrium following radium implantation and no carcinoma found in the surrounding tissues. Such cases have been reported by Martin,[15, 16] Bugbee,[17, 18] Schmitz,[12] Everett,[19] Mansur,[7] Behney,[20] and Goldblatt.[21]

Jaffe and his associates[22] report two patients with no evidence of recurrent disease, who had delayed upper urinary tract symptoms fourteen months after treatment. Everett[23] found evidence of obstructive lesions to the lower urinary tract in patients treated and apparently cured in 50 per cent of cases and in 15 per cent the lesions were sufficiently severe to be of clinical importance.

Wagner in 1858 (quoted by Graves and his associates[9]) found one-third of patients dying of carcinoma of the cervix showed considerable ureteral involvement. Behney[20] found dilated ureters in 65 per cent of 166 autopsies on patients dying with carcinoma of the cervix. Ureteral obstruction was found in 58 per cent of cases which were irradiated and in 72 per cent of the untreated cases. Drexler and Howes[8] found urinary tract obstruction in 81 per cent of 27 patients; and Herger and Schreiner[25] in 31 autopsies found 61 per cent to have gross pathological changes in the urinary tract. Graves and his associates[9] in 87 postmortem examinations found 79.3 per cent had hydronephrosis due to ureteral obstruction.

A clinical study by Jaffe and his associates[22] noted obstruction to one or both ureters in 70 per cent of 390 patients studied. Graves, Kickham, and Nathanson[9] found obstruction of ureters in over 70 per cent of 257 patients. Howes and Strauss[10] found 52 per cent ureteral obstruction in a clinical study of over 100 patients with carcinoma of the cervix.

In our study of 116 patients (Table II) with cervical carcinoma 62 (53.4 per cent) showed urinary tract obstruction on one or both sides. In 14 of this group the obstruction was of only a slight degree.

TABLE II. INCIDENCE OF URINARY TRACT OBSTRUCTION IN CARCINOMA OF THE CERVIX

GROUP*	BILATERAL	UNILATERAL		NONE	TOTAL
		RIGHT	LEFT		
I	0	0	2	1	3
II	1	1	2	13	17
III	6	12	7	23	48
IV	9	5	3	8	25
V	4	5	5	9	23
Total	20	23	19	54	116

*The grouping follows the Schmitz classification with a Group V added for those patients who received treatment at other clinics.

One Group I and one Group II case showed slight involvement of the left urinary tract shortly after the onset of treatment. This is believed to represent edema of the bases of the broad ligaments following the application of radium.

One Group II case which showed involvement of the left urinary tract two years after the original treatment is believed to represent extension of the disease.

The other Group I case and the Group II case with involvement of the right ureter studied five and seven months, respectively, after original treatment are believed to represent irradiation damage.

Adenocarcinoma of the Uterine Fundus

Hydronephrosis from adenocarcinoma of the fundus is less frequent than with the cervical lesions. This may be accounted for by the greater distance between the ureter and the fundus of the uterus, and also because the fundal lesions do not extend beyond the confines of the uterus as rapidly as cervical lesions.

In sixteen patients studied by intravenous urography before hysterectomy five showed partial obstruction of one or both ureters. In two there was gross extension of the disease to the tubes and ovaries; and in one patient there was an associated pelvic inflammatory disease and a fibromyoma of the uterus, the size of a four months' pregnancy. In the other two patients the cause of the obstruction was not apparent.

Pelvic Inflammatory Disease

Pelvic inflammatory disease not infrequently may cause urinary tract obstruction. The process may at times become progressive. Both pressure from

without and intrinsic inflammatory changes in the ureteral wall may be responsible.

Gill[26] has reported involvement of the ureteral wall by the inflammatory process. This was also pointed out by Shoemaker in his discussion of a paper by Kretschmer and Kanter.[2]

In pelvic inflammation, as in pyelitis of pregnancy, there is interference with peristalsis, causing atony of the ureter. Trattner[27] in studies with the hydrophorograph found that the effect of the toxins of *Bacillus coli* and Staphylococcus in great dilution had an excitant action on the ureter, but in heavy concentration caused a cessation of contractions, paralysis, and atony. He found the end result of an acute inflammatory process in the ureteral wall was either resolution, stricture formation, or atony of the ureter.

The incidence of urinary tract obstruction in pelvic infection varies greatly in the reports available. Stein and Rodgers[28] and Strumpf[29] concluded that urinary tract obstruction does not occur even in cases of extensive pelvic inflammatory disease. Kretschmer and Kanter[2] in a study of a case of tuboovarian abscess found a normal urinary tract.

Everett and Sturgis[1] found ureteral obstruction in 44.4 per cent of nine patients with chronic salpingitis; in 58.3 per cent of twelve patients with subacute salpingitis; and in 57.2 per cent of seven patients with pelvic abscess. The senior author in a previous study[3] found upper urinary tract dilatation in eight of fifteen patients with extensive pelvic inflammatory masses, and an abnormal delay in emptying of the kidney pelves in six additional patients.

In this study of 47 patients (Table III) with extensive pelvic inflammatory disease there was dilatation of the upper urinary tract in 23 patients (48.9 per cent); and an abnormal delay in drainage in five additional patients. In three of the patients follow-up study showed a progression of the urinary tract lesion. Ten of the 23 patients had urinary tract symptoms.

TABLE III. INCIDENCE OF URINARY TRACT OBSTRUCTION IN PELVIC INFLAMMATORY DISEASE

	BILATERAL	UNILATERAL		NONE	TOTAL
		RIGHT	LEFT		
Acute pelvic inflammatory disease	2	6	1	19	28
Chronic pelvic inflammatory disease	2	2	0	4	8
Pelvic abscess	4	4	1	1	10
Pelvic tuberculosis	0	1	0	0	1
Total	8	13	2	24	47

Fibromyoma of the Uterus

Ureteral obstruction in fibromyoma of the uterus is due to mechanical factors. The firm character of these tumors, which not infrequently extend high into the abdomen, will often cause sufficient pressure at the pelvic brim to cause a hydroureter and hydronephrosis. Small tumors which are intraligamentary can also be expected at times to compress the ureter against the pelvic wall below the pelvic brim.

Cabot[30] states that it is not rare to observe a hydronephrosis as a result of compression of the ureter by a multinodular fibroid. Strumpf,[29] and also Stein and Rodgers[28] have reported no change in the urinary tracts in their study of large fibroid tumors.

The incidence of ureteral obstruction in fibroid tumors was reported by Kretschmer and Kanter[2] as 70.8 per cent in 24 cases which extended above the pelvic brim; and 55.5 per cent in 11 cases of smaller fibroids. Everett and Sturgis[1] found dilatation of the urinary tract in 53.2 per cent of the cases studied in their series. The senior author in a previous report[3] of a study of

23 patients with fibroids found 16, or 66.6 per cent, with some evidence of ureteral obstruction. In nine patients the lesion was bilateral, and in all except two the tumor extended above the pelvic brim.

Payne in the discussion of a paper by Hundley and his associates[31] states he found an incidence of ureteral alteration in the form of obstruction, displacement, or both, in 66 (69 per cent) of 96 patients with benign pelvic tumors varying in size from a three and one-half to an eight months' pregnancy.

In our study of 139 patients (Table IV) with fibromyomas of the uterus there were 66 patients (47.5 per cent) with obstruction to one or both sides of the urinary tract. In 31 of these patients the obstruction was slight and not considered to be clinically significant. There were an additional number with delay in drainage and others with displacement of ureters, but no obstruction to the outflow of urine. Eight of the patients with involvement had tumors smaller than a four months' pregnancy. Twenty-one of the patients with ureteral obstruction had an associated chronic pelvic inflammatory disease found at the time of operation.

TABLE IV. INCIDENCE OF URINARY TRACT OBSTRUCTION IN FIBROMYOMAS OF THE UTERUS

	BILATERAL	UNILATERAL		NONE	TOTAL
		RIGHT	LEFT		
Fibromyomas of uterus	25	15	5	69	114
Fibromyomas of uterus with pelvic inflammatory disease	8	6	7	4	25
Total	33	21	12	73	139

Prolapse of the Uterus

A century ago Virchow first noted the presence of hydronephrosis and hydroureter at autopsy examination of patients dying with complete prolapse of the uterus. Various theories have been advanced as causes of ureteral obstruction in prolapse of the uterus.

Halban and Tandler quoted by Wallingford[32] found: kinking of urethra with stasis of urine and cystocele; intramural stretching of the ureters in the bladder wall with stenosis; and compression of the ureters outside the bladder.

Schmitz and Laibe[33] concluded that, as the uterus descends, the posterior bladder wall is carried along causing torsion of the ureters which is followed by circulatory disturbances, edema, and subsequently blockage of the ureters.

Frank[34] in the study of a fatal case concluded that the ureters were occluded by tension and compression caused by the uterine arteries. The ureters were tremendously dilated down to the point of crossing the uterine arteries, but below this point the caliber of the ureters was approximately normal. Wallingford[32] and Wosika and Maher[35] came to a similar conclusion.

Danforth[36] found that the vesical ends of the ureters are pressed upon by the hiatus genitalis in complete prolapse with resulting narrowing of the lumen at its lower end.

Lieberthal and Frankenthal[37] made x-ray studies with the catheters in place and concluded: the broad ligament with its contained fibrous bands which are attached laterally to the pelvic brim and medially to the cervix and corpus uteri forms a sling over the ureter and pulls it downward when the uterus descends.

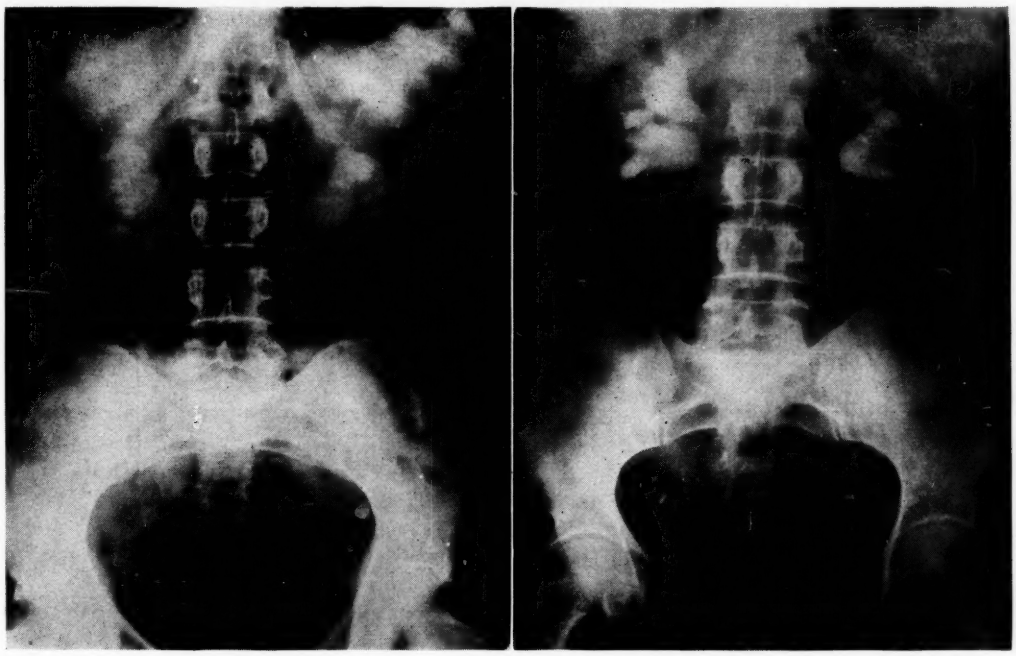
The incidence of urinary tract involvement will depend on the degree of prolapse and the duration of prolapse without the support of a pessary. Halban and Tandler, quoted by Wallingford,[32] found dilated ureters in 15 of 23 cadavers with complete prolapse, or 65.2 per cent. Wallingford presented six cases of prolapse with urinary tract obstruction. Lieberthal and Frankenthal[37] found

urinary tract change in 5 of 10 cases of prolapse studied. Everett and Sturgis[1] found urinary tract obstruction in 2 of 4 cases with procidentia. Kretschmer and Kanter[2] found bilateral urinary tract dilatation in 1 of 4 cases of prolapse studied. Wosika and Maher[35] in a study of 600 cases of hypertension found seven to have a long-standing prolapse of uterus with obstruction to the lower urinary tract.

In our study of 29 patients with large cystocele, 23 had uterine prolapse of varying degrees, with the uterus coming completely out of the vagina in 9 patients. There were 11 patients who showed mild hydronephrosis and hydroureter or delayed drainage from the upper urinary tracts. Only one patient showed a marked degree of hydronephrosis:

Mrs. A. T., aged 52 years, was admitted to the Jefferson Hospital on Jan. 16, 1948, with complaint of a mass protruding from the vagina for the past six months, and frequency of urination for several years. On examination the patient was found to have procidentia uteri, umbilical hernia, and left inguinal hernia. Intravenous urography on Jan. 20, 1948, showed a marked bilateral hydronephrosis, which was somewhat greater on the right than on the left. Both ureters were also significantly dilated. A vaginal hysterectomy and posterior colporrhaphy were done on Jan. 23, 1948.

Recheck intravenous urogram on Feb. 2, 1948, showed marked improvement in hydronephrosis (Fig. 3). Subsequent studies have revealed further improvement.



A. *B.*

Fig. 3.—*A*, Intravenous urogram before operation showed a marked bilateral hydronephrosis. *B*, Re-examination ten days after operation showed a marked improvement in the hydronephrosis.

Discussion

It is interesting to observe that in the group of patients with benign pelvic lesions, unilateral urinary tract dilatation occurred much more frequently on the right side. Similar findings have been noted by many investigators in the study of patients during pregnancy and suggests that the same mechanical factors may be responsible in both instances.

Although our follow-up studies are by no means complete, a few observations of our own confirm the findings of others (Everett and Sturgis[1] and Kretschmer and Kanter[2]) that the urinary tract dilatation is reversible and disappears within several weeks after the tumor has been removed. Five patients with benign ovarian tumors were restudied by intravenous urography ten days to three weeks after removal of the tumor and in each instance there was marked improvement. Eight patients with fibromyomas of the uterus were restudied after operation by means of intravenous urography and five showed a complete return to normal and three showed marked improvement.

In many instances there were no symptoms referable to the urinary tract even in the presence of marked pyelectasis. These silent lesions were found most frequently in association with the benign tumors.

Summary and Conclusions

1. In a study of the urinary tract by means of intravenous urography of 379 patients with various benign and malignant gynecologic lesions, there was found to be urinary tract obstruction of a greater or less degree in 49.4 per cent of the patients.

2. Most extensive pelvic gynecologic lesions may cause sufficient pressure on the ureters to interfere with the outflow of urine and may result in hydronephrosis and in some cases may produce serious renal damage.

3. A severe degree of hydronephrosis may be present with no symptoms referable to the urinary tract. This was found especially in patients with ovarian tumors and with fibromyomas.

4. The urinary tract lesion may be progressive in instances of pelvic inflammatory disease which is an important consideration in the plan of treatment.

5. A survey of the urinary tract is an important adjunct to the preoperative evaluation of the patient with an extensive gynecologic lesion.

TABLE V. URINARY TRACT OBSTRUCTION IN BENIGN AND MALIGNANT GYNECOLOGIC LESIONS

	BILATERAL	UNILATERAL		NONE	TOTAL	PER CENT INVOLVED
		RIGHT	LEFT			
Benign ovarian tumors	5	5	1	8	19	57.8
Malignant ovarian tumors	6	3	0	4	13	69.2
Carcinoma of cervix	20	23	19	54	116	53.4
Adenocarcinoma of fundus	3	2	0	11	16	31.2
Pelvic inflammatory disease	8	13	2	24	47	48.9
Fibromyoma of uterus	33	21	12	73	139	47.5
Cystocele and uterine prolapse	4	7	0	18	29	37.9
Total	79	74	34	192	379	49.4

References

1. Everett, Houston S., and Sturgis, William J.: Urol. & Cutan. Rev. 44: 638-641, 1940.
2. Kretschmer, H. L., and Kanter, A. E.: J. A. M. A. 109: 1097, 1937.
3. Montgomery, J. B.: Pennsylvania M. J. 47: 1080, 1944.
4. Hofbauer, J.: Bull. Johns Hopkins Hosp. 42: 118-153, 1928.
5. Hundley, J. Mason, Siegel, Isadore A., Hachtel, Frank W., and Dumler, John C.: Surg., Gynec. & Obst. 66: 360, 1938.
6. Kelly, Howard A., and Burnam, Curtis F.: Diseases of the Kidneys, Ureters and Bladder, New York, 1914, D. Appleton & Company, p. 526.
7. Mansur, Edward E.: Radiology 43: 147, 1944.
8. Drexler, Leo S., and Howes, William E.: AM. J. OBST. & GYNEC. 28: 197, 1934.

9. Graves, Robert C., Kickham, C. J. E., and Nathanson, Ira T.: J. Urol. **36**: 617, 1936.
10. Howes, William E., and Strauss, Hymen: Am. J. Roentgenol. **41**: 63, 1939.
11. Carson, William J.: Ann. Surg. **82**: 142, 1925.
12. Schmitz, Henry: Am. J. Roentgenol. **24**: 47, 1930.
13. Martin, Charles L., and Rogers, Fred. T.: Am. J. Roentgenol. **15**: 336, 1926.
14. Martin, Charles L., and Rogers, Fred. T.: Am. J. Roentgenol. **16**: 215, 1926.
15. Martin, Charles L.: Am. J. Roentgenol. **20**: 30, 1928.
16. Martin, Charles L.: J. A. M. A. **91**: 1537, 1928.
17. Bugbee, H. G.: J. Urol. **32**: 439, 1934.
18. Bugbee, H. G.: J. Mt. Sinai Hosp. **4**: 712, 1938.
19. Everett, Houston S.: Am. J. Obst. & Gynec. **28**: 1-10, 1934.
20. Behney, Charles A.: Am. J. Obst. & Gynec. **26**: 608, 1933.
21. Goldblatt, Myron E.: Urol. & Cutan. Rev. **47**: 632, 1943.
22. Jaffe, Henry J., Meigs, Joseph V., Graves, Roger C., and Kickham, Charles J. E.: Surg., Gynec. & Obst. **70**: 178, 1940.
23. Everett, Houston S.: Am. J. Obst. & Gynec. **38**: 889, 1939.
24. Morton, Daniel G.: California & West. Med. **42**: 345, 1935.
25. Herger, Charles C., and Schreiner, Bernard F.: Surg., Gynec. & Obst. **43**: 740, 1926.
26. Gill, R. D.: West Virginia M. J. **37**: 337, 1941.
27. Trattner, Harry R.: J. Urol. **28**: 1, 1932.
28. Stein, Arthur, and Rodgers, Mortimer: Surg., Gynec. & Obst. **55**: 490, 1932.
29. Strumpf, Irving J.: Am. J. Obst. & Gynec. **26**: 857, 1933.
30. Cabot, Hugh: Modern Urology, Philadelphia, 1936, Lea & Febiger Co., Vol. II, p. 422.
31. Hundley, J. Mason, Diehl, William K., and Diggs, Everett S.: Am. J. Obst. & Gynec. **44**: 858, 1942.
32. Wallingford, Arthur J.: Am. J. Obst. & Gynec. **38**: 489, 1939.
33. Schmitz, Henry, and Laibe, Joseph E. F.: Urol. & Cutan. Rev. **33**: 290, 1929.
34. Frank, Robert T.: Am. J. Obst. & Gynec. **22**: 270, 1931.
35. Wosika, P. H., and Maher, C. C.: Am. J. Obst. & Gynec. **38**: 684, 1939.
36. Danforth, William C.: S. Clin. North America **18**: 213, 1938.
37. Lieberthal, Frederick, and Frankenthal, Lester: Surg., Gynec. & Obst. **73**: 828, 1941.

Discussion

DR. FRANKLIN L. PAYNE.—Dr. Long's quotation, that approximately 70 per cent of 96 patients with benign pelvic tumors showed urographic evidence of alterations arose from a report that appeared in *Radiology* for February, 1944. We did this study in association with Dr. George Chamberlin of the Department of Radiology in the Hospital of the University of Pennsylvania. Intravenous urograms were obtained both pre- and postoperatively. All of the tumors were benign and all were at least 10 cm. in diameter. Uterine myomas were present in 77 patients, ovarian cysts in 14 patients, and 5 had both myomas and a cyst. Of the entire group, 66 (68.7 per cent) showed roentgen evidence of ureteral obstruction, displacement, or both. These changes were observed in 72 per cent of the patients with myomas, 43 per cent of those with cysts, and 80 per cent of the ones who had both cysts and myomas.

The tumors ranged in size from 10 to 30 cm. in diameter as measured following their removal. While the larger tumors produced pressure changes frequently, we found no relation between the degree of dilatation and the size of the tumors. Indeed, some of the largest tumors caused no ureteral changes. On the other hand, the position and the degree of fixation of the tumors in the pelvis was important. Both the highest percentage of alterations and the most marked changes were observed with the impacted and the intraligamentary growths, of which 84 per cent showed abnormal urographic manifestations. These aberrations seemed to be similar to those associated with pregnancy, but rarely were they so pronounced. In no instance did complete ureteral absence of function occur, such as we see in malignant disease so frequently. These observations raise the question as to whether there was some other explanation for the marked changes associated with the granulosa-cell tumor that Dr. Long cited.

An interesting phase of the study occurred in the comparison of the preoperative and the postoperative urogram. The latter were made from eight to sixteen weeks following operation and in every instance a return to normal function was demonstrated, to offer reassuring evidence of the reversibility of these changes when they are caused by benign removable pelvic tumors.

Both the study by Drs. Montgomery and Long and our work contain numerous practical implications, some of which Dr. Kimbrough has discussed. As to benign pelvic neoplasms, the pressure of a moderate-sized or a large impacted or intraligamentary tumor indicates a preoperative urographic study including cystoscopic examination and an intravenous urogram. Should this investigation reveal ureteral displacement, distortion, or both, the introduction of ureteral catheters is advisable as the preliminary step to pelvic laparotomy. While this is important with such a myoma, it is even more so when the removal of an intraligamentary cyst is to be undertaken because of the increased danger of ureteral damage that accompanies this type of operation, particularly if the cyst is to be removed without rupture.

DR. LEON REIDENBURG.—I should like to ask a question concerning the effect of these findings on the blood chemistry and kidney function in this series of patients.

DR. LONG (Closing).—Regarding the discussion of the patient with the granulosa-cell tumor, I realize it would be difficult to prove that the dilatation of the urinary tract was due to hormonal influence. However, a very interesting experiment has been carried out by Von Wagonen and Jenkins. They performed cesarean section on Rhesus monkeys during the early months of pregnancy, removing the fetus and leaving the placenta in situ. The dilatation of the urinary tract not only persisted but actually progressed until term, when the placenta was expelled. They concluded that the dilatation of the urinary tract in pregnancy is dependent upon the endocrine function of the placenta.

To answer the question concerning the influence on blood chemistry: in most instances where the changes are reversible and serious damage has not occurred, one would not find retention of nitrogenous waste products; however, when the ureteral obstruction is permanent and the upper urinary tract lesion is progressive, as is often seen in malignant tumors, serious kidney damage and its sequelae occur.

Arenas, Normando, and Blanchard, Oscar: The Value of Colpocytology in Diagnosis and Treatment of Dysmenorrhea and Mastodynia, An. brasil. de ginec. **27**: 205, 1949.

The authors report on a series of thirty-two patients having dysmenorrhea and ten exhibiting premenstrual mastodynia. They employed the Shorr stain in evaluation of vaginal smears in these patients. In the group of dysmenorrheic cases they observed a marked estrogenic reaction in the smears during the second half of the menstrual cycle among 84 per cent of this series. They found that eight of the ten patients exhibiting mastalgia in the second half of the menstrual cycle had a marked estrogenic response.

The administration of 30 mg. of progesterone given in a three-day course of 10 mg. daily, beginning on the calculated tenth day before the appearance of the menstrual period, provided relief in 78 per cent of the dysmenorrheic cases and 90 per cent of the series of cases of mastodynia.

The writers conclude the use of vaginal smears contributes to a more correct diagnosis and aid in treatment control. C. E. FOLSOME.

ORAL BASAL TEMPERATURES IN ABORTION AND ECTOPIC PREGNANCY

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PROGESTIN and estrogen therapy in abortion continues as a controversial issue. Laboratory studies have failed to establish a deficiency of these hormones in the human being as an important etiological factor in the spontaneous termination of early pregnancy. Clinical investigations have accumulated a wide divergence of opinions as to the value of replacement therapy. Since recent observations have disclosed that the thermal regulating mechanism of the body is directly influenced by progesterone and estrogen, a clinical study of the oral basal temperature curve of patients with threatened and inevitable abortion as well as ectopic pregnancy forms the basis of this study.

My study of the oral basal temperature curves of 425 women during normal pregnancy is presented in a previous report.[1] In the event of pregnancy, the postovulatory temperature rise continues during the first trimester. The corpus luteum regresses at the end of the third month of pregnancy and it is at this time that the basal temperature elevation shows a gradual fall, in most cases, so that the estrogen (preovulatory) level is attained by the fourth or fifth month. Since the elevation of basal temperature due to progesterone is present only during the first trimester of pregnancy, this affords an excellent indicator of any significant metabolic changes occurring in threatened and inevitable abortion.

Present Study

The illustrative cases presented in this study are from a series of twenty-seven women who had been taking their temperatures prior to pregnancy and subsequently were threatened with or continued to have a spontaneous termination early in gestation. Among the twenty-seven women were two requiring operation for ectopic pregnancy. Instruction to the patient and the technique of recording temperatures have been outlined in detail in a previous clinical study of oral basal temperatures.[2]

Results

CASE 1.—L. L. (Fig. 1), aged 33 years, was a gravida ii whose first pregnancy three years before ended in spontaneous abortion at approximately two and one-half months. The last menstrual period of the second pregnancy began Jan. 9, 1948, and the pregnancy progressed uneventfully until February 18 when uterine cramps and bleeding occurred for a period of four successive days. There was no perceptible change in the oral basal temperature curve prior to the onset or during the period of threatened abortion. The temperatures remained at a relatively high level during the symptomatic period. At a later date with a normally progressing pregnancy, the temperatures showed a wider variation and a gradual fall of the curve which is normal for the period of gestation. The absence of any significant change in the curve showed a stable thermal metabolism indicating progesterone production and utilization. Treatment consisted of bed rest for a period of ten days and thyroid extract orally during the remainder of the pregnancy. The pregnancy continued uneventfully to term and delivery of a normal living baby.

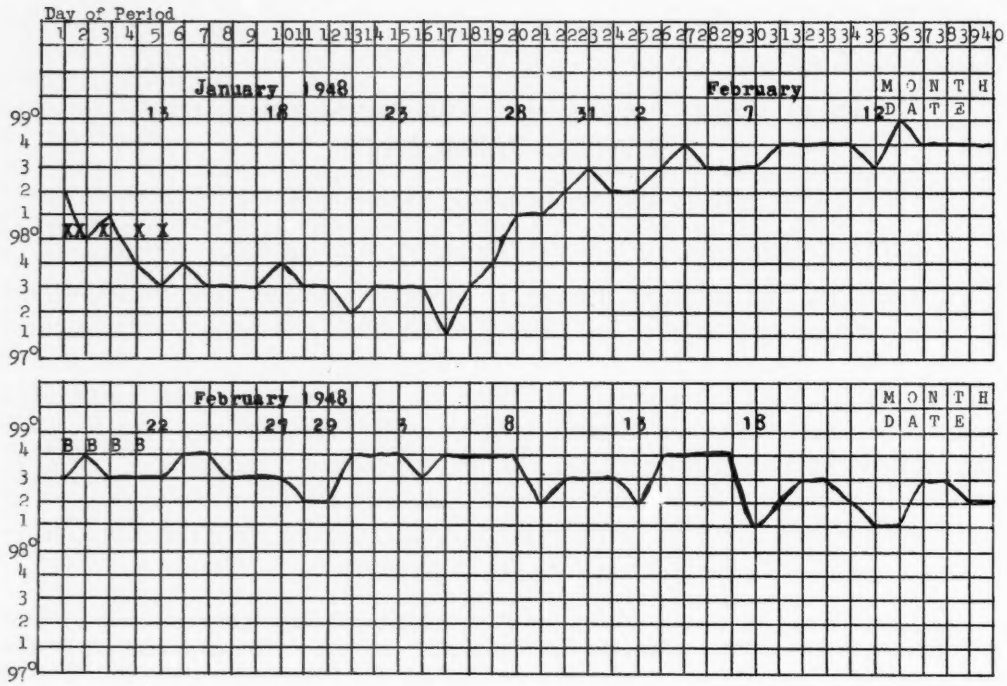

Fig. 1.—L. L., No. 520913. Oral basal temperatures in threatened abortion.

CASE 2.—G. H. (Fig. 2). Here is recorded the curve of a patient, aged 30 years, whose first pregnancy ended in spontaneous abortion on Nov. 15, 1948. The abortion ended abruptly after only two days of premonitory symptoms of uterine cramps and bleeding. The products of conception were identified by gross examination. There was a conspicuous absence of any alteration of the temperature curve during the preabortal period which would serve as a warning signal of impending disaster to the pregnancy. There was no significant change in the basal body temperature level and consequently no suggestion of progesterone deficiency. Furthermore, there were no temperature changes during the symptomatic phase which would aid in the differential diagnosis between threatened and inevitable abortion. It was not until the fifth postabortal day that the temperature curve returned to the preovulatory or estrogen level.

The last menstrual period prior to abortion began Sept. 27, 1948. Ovulation on the ninth day of the cycle was followed by a temperature rise which remained elevated in the presence of pregnancy. Following spontaneous abortion there was a ten-day interval from the time the basal temperature returned to a low level (November 20) until the next ovulation (November 30). A normal corpus luteum phase of fifteen days was followed by menstruation with ovulation again occurring on the tenth day (December 24) of the cycle. The immediate establishment of the normal menstrual cycle and biphasic thermal curve gives further support to the opinion that estrogen and progesterone deficiency did not exist in this patient.

CASE 3.—J. T., aged 31 years, gravida iii, is now classed as an habitual aborter. The temperature pattern in Fig. 3 is the curve during her third spontaneous abortion. A normal menstrual period lasted for four days beginning Dec. 4, 1947. Bleeding with cramps occurred daily from January 13, and on January 19, the products of gestation were removed from the vaginal canal. There were no characteristics of the oral basal temperatures prior to January 13 which would predict threatened or inevitable abortion. The uterine bleeding was over a period of six days prior to the expulsion of the pregnancy in contrast to Case

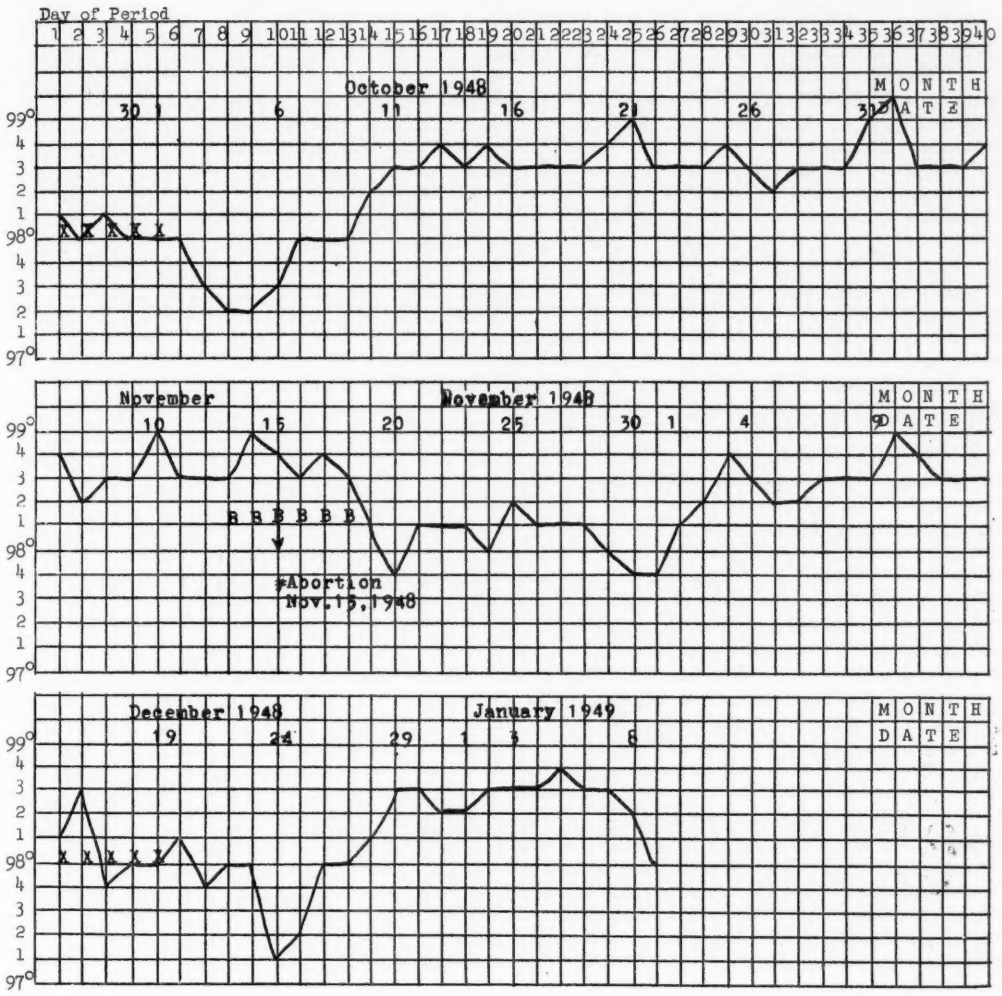

Fig. 2.—G. H., No. 536700. Oral basal temperatures in inevitable abortion.

G. H. (Fig. 2) in whom the preabortal bleeding lasted two days. As a general rule, the longer uterine bleeding is present in the preabortal phase, the earlier the temperature returns to a low level following abortion. It is interesting to note the ovulatory rise occurring just twelve days (February 1) after the immediate postabortal fall in the basal temperature with a normal menstrual flow at the end of thirty days (February 19). Again, a normal menstrual cycle followed as characterized by the biphasic basal temperature curve with ovulation occurring on the eleventh day of the cycle.

Case 4.—V. W. (Fig. 4), aged 34 years, gravida ii. This chart illustrates a slight fluctuation in basal temperatures prior to the onset of uterine cramps and bleeding which terminated in spontaneous abortion. These temperature changes are not considered unusual for they may be present during the first trimester of normal pregnancy. The temperature at no time went below 98° F. The temperature returned to the estrogen level on the third postabortal day. A normal menstrual cycle immediately followed with ovulation and a normal menstrual flow in the course of the following twenty-eight days. The immediate occurrence of a normal menstrual cycle as indicated by ovulation, menstruation, and the biphasic character of the temperature curve is considered as additional evidence of an adequate endocrine function.

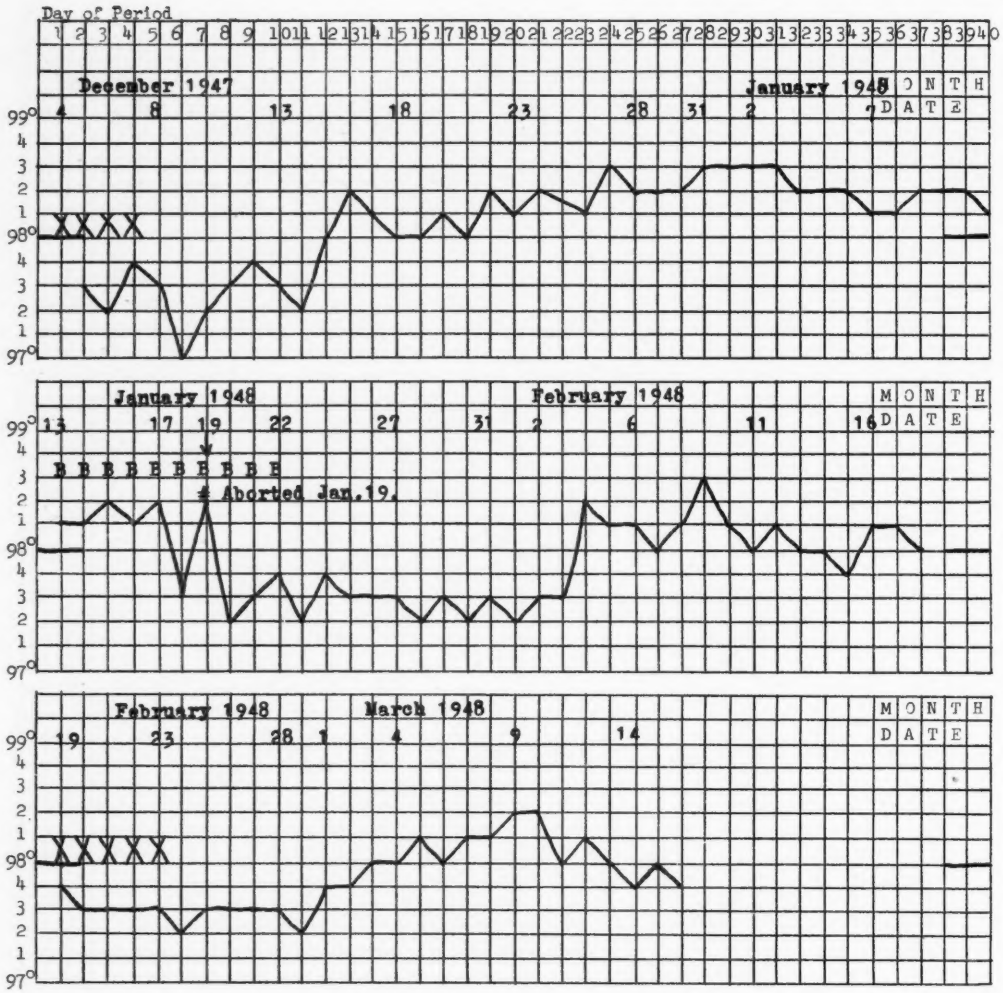

Fig. 3.—J. T., No. 525488. Spontaneous abortion. Last menstrual period Dec. 4, 1947.

CASE 5.—M. E. Mc. (Fig. 5), 26-year-old primigravida, did not record basal temperatures until spotting first occurred on Oct. 5, 1947. The last menstrual flow began Aug. 18, 1947. Intermittent periods of uterine cramps and bleeding occurred during the subsequent nineteen days. Several large uterine fibroids were present. Wide variations of the temperature curve were noted during the nineteen days of cramps and bleeding. A diagnosis of inevitable abortion was made clinically before the passage of the conceptus. Speculation as to the cause of the temperature variation involves not only the endocrine viewpoint but absorption of the decomposition products of conception as well as changes in the uterine fibroids. These considerations could account for the relatively longer period necessary for return of the temperature to the low estrogen range. Significant fluctuations of the temperature curve as illustrated in this case are not present in most cases of inevitable abortion.

CASE 6.—A. H. (Fig. 6) threatened to abort near the end of the first trimester. There were no changes in the basal temperature curve prior to or during the bleeding period as compared to those cases already illustrated in which spontaneous abortion terminated the pregnancy. A slight fall with fluctuations of the curve was evident but this is seen in normal pregnancy near the end of the third month as well as in some cases which abort spontaneously.

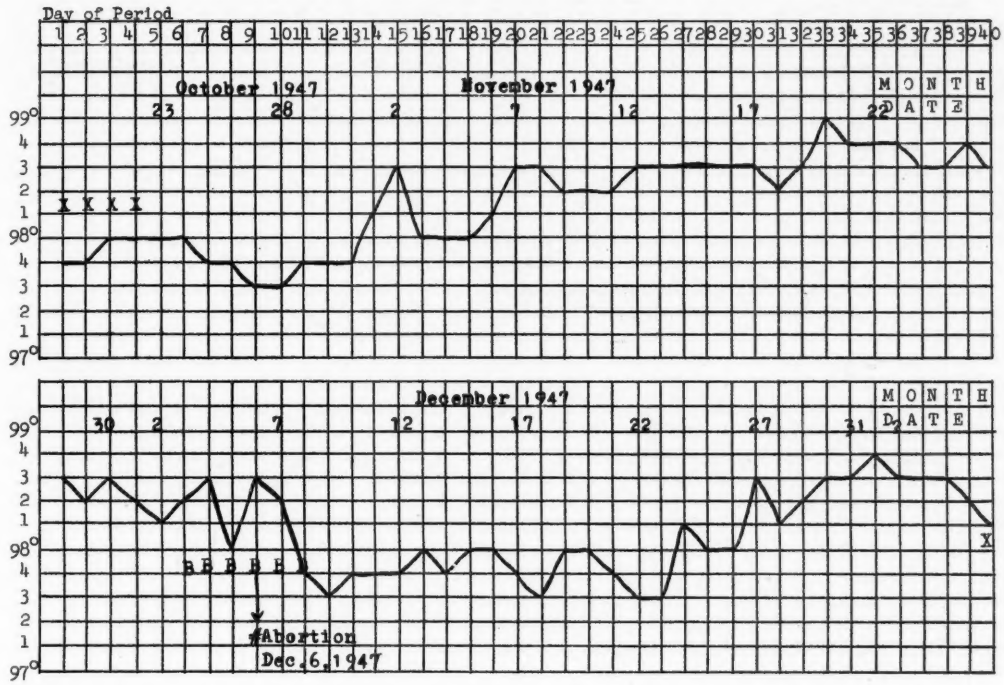

Fig. 4.—V. W., No. 516894. Oral basal temperatures in inevitable abortion.

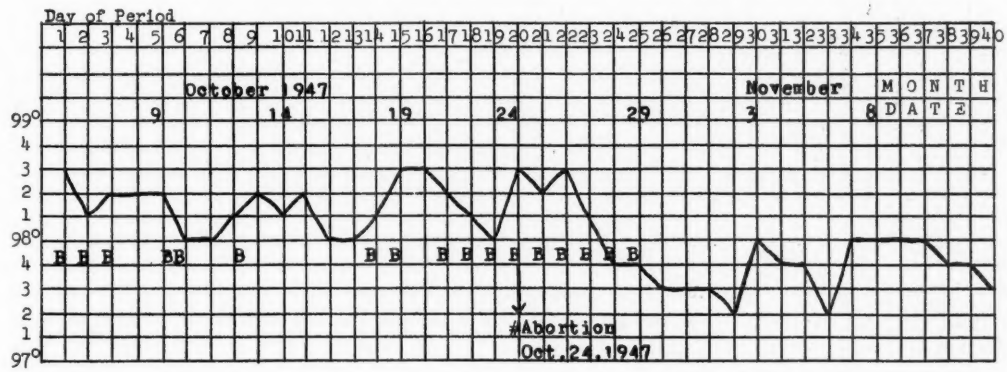

Fig. 5.—M. E. Mc., Oral basal temperatures in spontaneous abortion.

CASE 7.—A. A. (Fig. 7), aged 34 years, gravida iii. Variation of the basal temperature curve may occur during pregnancy without symptoms of abortion. The patient presented herself for prenatal care on Dec. 6, 1947. She had been recording daily basal temperatures and had been placed on thyroid extract prior to the present pregnancy. Thyroid therapy has been shown by Montgomery and Stewart,[2] Delfs and Jones[3] and others as the most important single therapeutic agent in the treatment of abortion among pregnant patients of low fertility. The patient had rightfully assumed pregnancy on the basis of the temperature curve. The last menstrual period began Oct. 27, 1947, and the pregnancy had progressed uneventfully to date. This was her third pregnancy, the other two having terminated in spontaneous abortion.

During the period from December 16 to January 5 the temperature curve showed wide fluctuations but there were no signs or symptoms of threatened abortion. Variation

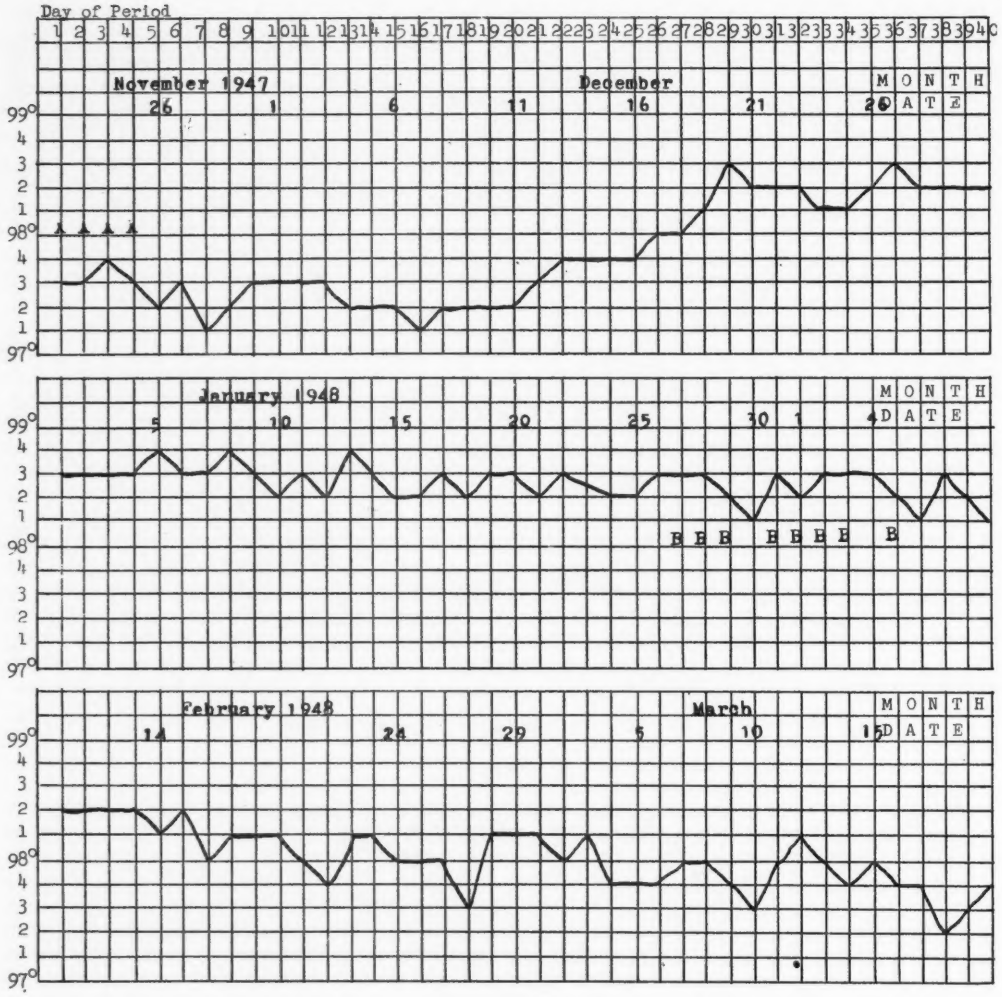

Fig. 6.—A. H., No. 487682. Oral basal temperatures in threatened abortion.

of the temperature curve does not preclude abortion although unjustified apprehension might arise at the time as to the possibility of spontaneous abortion if an erroneous conclusion is formed from the basal temperature. The patient continued uneventfully in this pregnancy and delivered at term a normal living baby.

CASE 8.—Fig. 8 illustrates an interesting problem in which oral basal temperatures furnished valuable diagnostic aid. It involved the differential diagnosis between delayed menstruation and abortion. M. R., aged 24 years, gave a history of two previous spontaneous abortions. At the first visit on July 22, 1947, she was requested to record daily oral basal temperatures because of irregularity of menstruation. Thyroid extract was administered orally. The patient was seen on September 19 because of uterine cramps and bleeding and she was quite certain that the bleeding was due to a third abortion and not to menstruation. No evidence of any products of conception was found in the clots passed. As bleeding continued, it became more apparent to the patient that it might well be menstruation. However, on close questioning she stated that this episode was identical in every respect with the suspected previous miscarriages. It has been shown that the duration of the corpus luteum temperature phase is relatively constant and continues for approximately fourteen to sixteen days.[1] In a small number of patients it may extend as

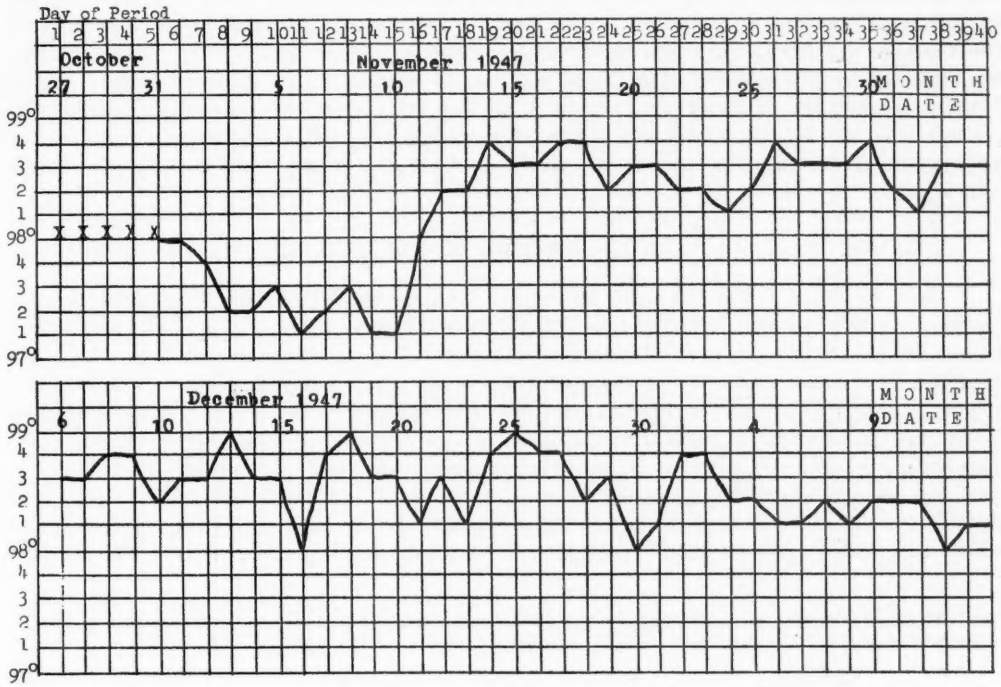

Fig. 7.—A. A., No. 559471. Oral basal temperatures during pregnancy.

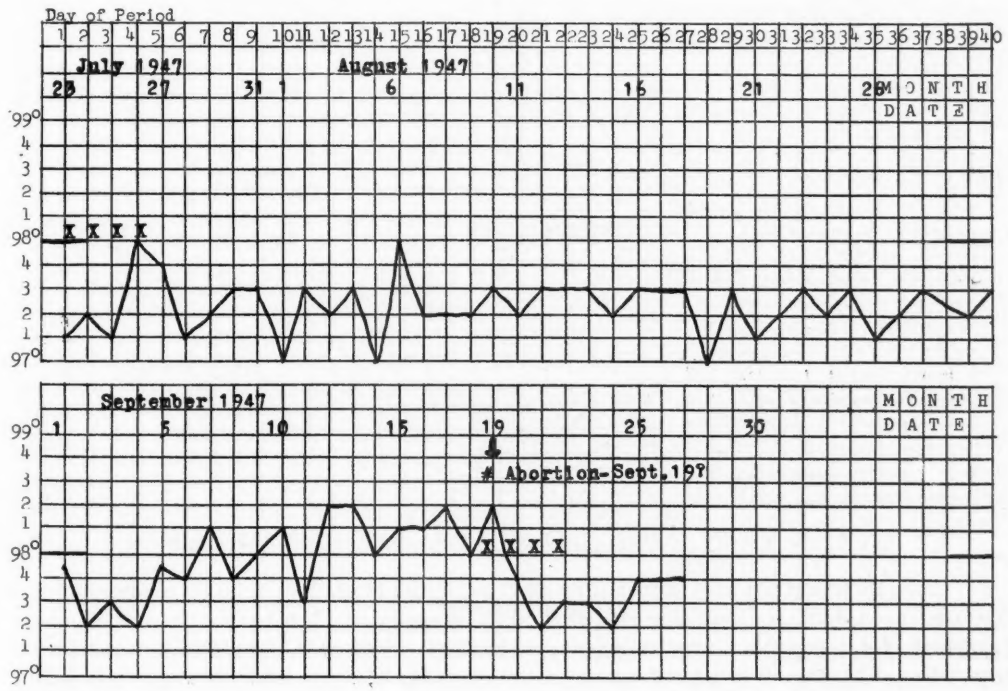

Fig. 8.—M. R., No. 420488. Delayed menstruation diagnosed spontaneous abortion.

long as nineteen days. From examination of the basal temperature chart, it was significant that this patient had ovulated on September 4, and this was followed by an elevation of the temperature for the next fourteen days, indicative of the corpus luteum phase. Menstruation occurred on September 19 as one would suspect from the temperature curve. From the evidence at hand and the clinical history, one might reasonably assure this patient that she is not a habitual aborter. Progesterone and even estrogen replacement therapy in the event of an actual pregnancy in this patient might apparently give excellent results.

Two oral basal charts in the presence of ectopic pregnancy are shown.

CASE 9.—K. W. (Fig. 9), aged 30 years, primigravida had an ectopic gestation located in the outer third of the Fallopian tube. The differential diagnosis was between ectopic pregnancy and corpus luteum cyst. Uterine bleeding and lower abdominal pain began with the expected date of menstruation on Oct. 22, 1947. Intermittent spotting and abdominal discomfort continued during the next thirty days. Operation and pathological examination revealed the presence of a tubal pregnancy. The temperature chart was of no value in the differential diagnosis. In the presence of a corpus luteum cyst it is reasonable to speculate that the temperature would continue at an elevated level. It is of interest, however, with the onset of uterine bleeding, and presumably death of the gestation, the temperatures varied widely but tended to be at a lower level than during the preceding corpus luteum phase.

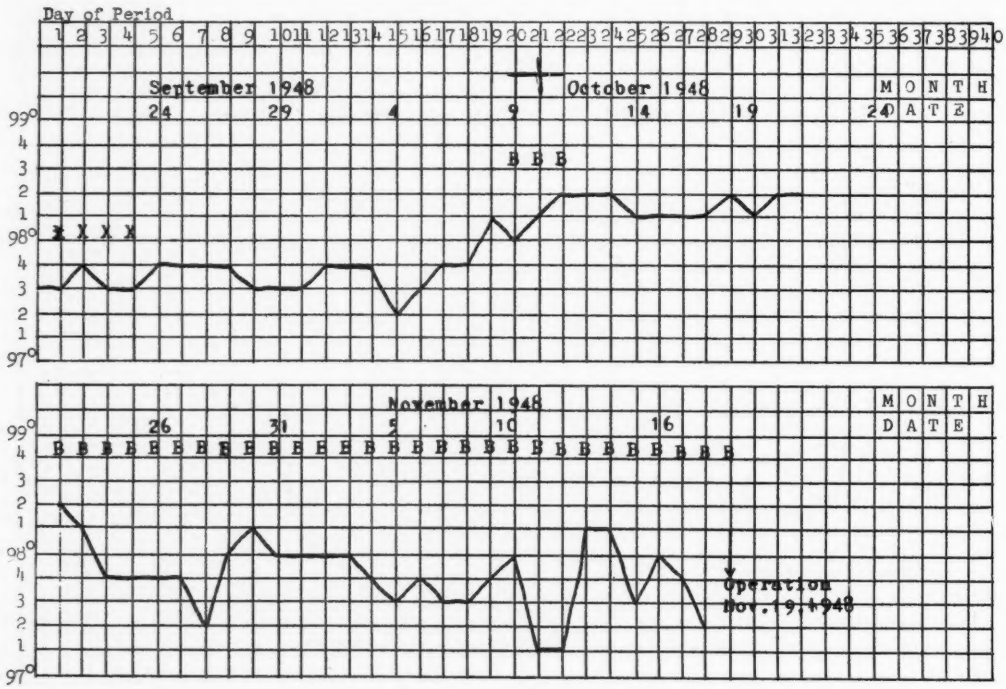

Fig. 9.—K. W., No. 543120. Oral basal temperatures in tubal pregnancy.

CASE 10.—Contrast the temperature chart of D. G. (Fig. 10), aged 34 years, who was operated upon Jan. 12, 1949, for ruptured tubal pregnancy. The patient had been under treatment for irregular menstruation and infertility. The last normal menstrual period began Dec. 6, 1948. The patient was admitted because of acute abdominal symptoms and evidence of intraperitoneal hemorrhage. Operation was performed immediately after admission. The operative diagnosis of ruptured tubal pregnancy was confirmed by pathological examination, the rupture occurring in the inner third of the tube. The temperature

curve remained unchanged prior to admission to the hospital. The basal temperature chart was valuable evidence in support of the clinical diagnosis of pregnancy but was of no value as a differential aid as to location. A Friedman test performed the day following surgery was positive. Uterine bleeding and passage of the decidual cast occurred at the end of the second postoperative day. With a short duration of symptoms and sudden termination of pregnancy, it was several days before the Friedman test became negative and the temperature did not return to the preovulatory level until the ninth postoperative day. This chart illustrates that the temperature curve will continue without change until the complication of the early pregnancy occurs whether the pregnancy is extrauterine or intrauterine.

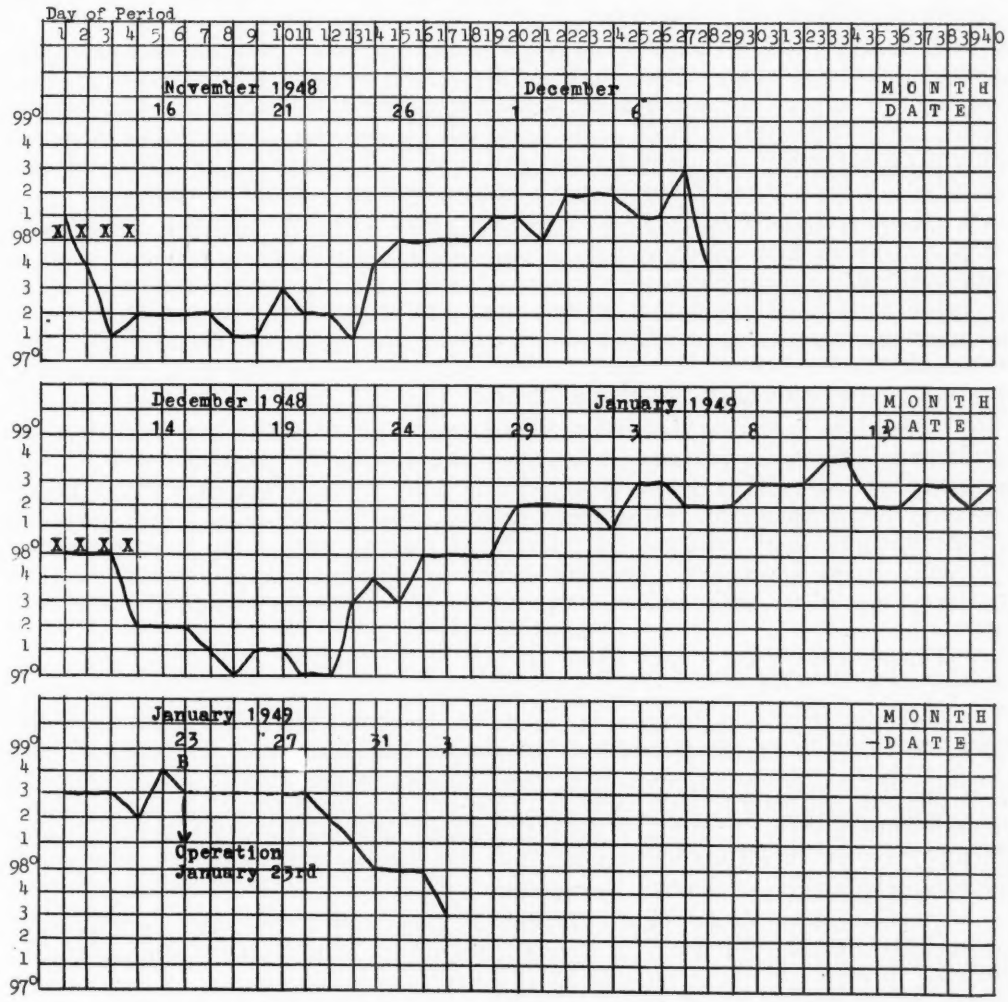

Fig. 10.—D. G., No. 300548. Oral basal temperatures in tubal pregnancy.

Discussion

Clinical observations have shown that rhythmic variations of the basal body temperature during the normal menstrual cycle are closely associated with ovarian secretion. The normal curve is biphasic with a low estrogen curve from menstruation to ovulation, followed by a relative hyperthermic plateau which continues until the succeeding menstrual flow. Pregnandiol

tests are negative and endometrial biopsies show proliferative stages if these tests are made prior to the thermal shift indicative of the corpus luteum phase of the cycle. In the presence of pregnancy and persistence of the corpus luteum, excretion of pregnandiol in the urine continues and decidual changes of the endometrium are evident. The elevated basal temperature continues during the first three months of gestation which suggests that progesterone is intimately associated with the thermal regulating system. It logically follows that progesterone deficiency as a cause of spontaneous abortion should be evident by changes in the basal body temperature curve. This is the basis of the present study and it is applicable only during the first trimester of pregnancy when the temperature is elevated. It is during this period that the incidence of abortion is highest.

When this study was undertaken, it was anticipated that certain peculiarities of the temperature curve might be discernible which would serve as a warning sign of impending abortion before the occurrence of clinical signs and symptoms. Any procedure which would foretell threatened or inevitable abortion would be extremely valuable for patients who had previously aborted. An invaluable basis for the efficacy of replacement therapy would be available.

Comparison of Case 1, L. L. (Fig. 1), and Case 6, A. H. (Fig. 6), shows a complete absence of any variation in the oral basal temperature curve prior to the onset of clinical signs of threatened abortion. In each case the relative hyperthermic curve continued without any significant alteration before the onset of uterine cramps and bleeding. Even during the period of bleeding the curve continued as in normal pregnancy. The basal temperature curve, therefore, is of no prognostic value in threatened abortion.

Attention was next directed to the characteristics of the basal curve in the differential diagnosis between threatened and inevitable abortion. If the final outcome of the case of a pregnant patient with signs of abortion could be accurately predicted from the oral temperatures, then the management of inevitable abortion would be simplified. Replacement therapy would be inadvisable and in many cases prolonged disability could be eliminated. Active therapeutic measures would be indicated as long as the temperatures designated threatened abortion.

The charts (Figs. 1 and 6) of women with threatened abortion are to be compared with those in whom the pregnancy terminated in spontaneous abortion. The basal temperature curve of G. H. (Fig. 2) shows no distinguishing characteristics prior to or during inevitable abortion. Patients J. T. (Fig. 3) and V. W. (Fig. 4) demonstrated no temperature changes prior to uterine cramps and bleeding although there is a fall one day before passage of the products of conception. The temporary drop preceding the day of abortion is not uniformly present in all cases of inevitable abortion as it is seen also in cases of threatened abortion and normal pregnancy.

In the case of A. A. (Fig. 7), wide fluctuations in the basal temperature are evident in the presence of a normal pregnancy. This patient spontaneously aborted during the first trimester of two previous pregnancies. If fluctuations in the basal curve are indicative of threatened or inevitable abortion, then there should have been undue concern for her and in other cases of this kind. Comparison of this chart with those of threatened and inevitable abortion illustrates that the oral basal temperature curve serves no useful purpose in the differential diagnosis between threatened and inevitable abortion.

The observation that the basal temperature did not fall to the preovulatory (estrogen) level before or during abortion is indicative of continued progesterone production and utilization. It is significant that, when the abortion was preceded by a short symptomatic period (Fig. 2), the temperature required a longer

time to return to the low estrogen level in the postabortal period than when the converse was in evidence (Fig. 3). The time factor is important in that the shorter the duration of symptoms indicative of a complication, the longer the time that is necessary for the temperature to return to a lower level. This is true in extrauterine pregnancy (Fig. 9). An analogous situation is present in the excretion of the chorionic gonadotropic hormone where the time factor enters into consideration. When a short interval of symptoms precedes the termination of a pregnancy, then the incidence of positive Friedman or Aschheim-Zondek tests is high. The recognition of the time element necessary for excretion of these hormones is further evidence of their presence in adequate amounts preceding the termination of the pregnancy.

The frequency of immediate re-establishment of a normal menstrual cycle following spontaneous abortion as characterized by ovulation, menstruation, and the biphasic character of the temperature curve is highly significant. This is considered as evidence of an adequate endocrine function.

Basal temperature charts are valuable aids in clinical diagnosis. Recently, I reported on the value of oral basal temperatures in the clinical diagnosis of early pregnancy.[1] A low estrogen basal temperature curve in the presence of amenorrhea is incompatible with pregnancy and has proved of great assistance in detecting errors in clinical diagnosis. An example has been presented in Case 8, M. R. (Fig. 8). Although this patient believed that an early pregnancy had terminated in spontaneous abortion, the basal temperature curve failed to support this supposition. The curve demonstrated the presence of a prolonged estrogen phase followed by a normal corpus luteum phase. Unquestionably, this was a case of delayed menstruation and not abortion. Many similar cases have been detected since basal temperatures have been used routinely at this institution.

Two cases of basal temperatures during tubal pregnancy have been presented. The relative hyperthermic phase of the temperature continues in the presence of pregnancy regardless of the location. As in other diagnostic aids for pregnancy, such as the Friedman and Aschheim-Zondek tests, the basal temperature curve fails to differentiate between intrauterine and extrauterine pregnancy.

Conclusions

1. The estrogen curve of oral basal body temperatures is low, while progesterone causes an elevation.

2. There is no perceptible change in the basal temperature curve during the preabortal period which would serve as a warning of impending disaster to the pregnancy. There are no characteristic temperature changes during the symptomatic phase which would aid in the differential diagnosis of threatened and inevitable abortion. These observations are indicative of a stable thermal metabolism including estrogen and progesterone utilization.

3. In most cases following spontaneous abortion there is an immediate establishment of a normal menstrual cycle as indicated by ovulation, menstruation, and the biphasic character of the temperature curve. This is additional evidence of the presence of an adequate endocrine function.

4. In abortion and tubal pregnancy there is an indirect time relation between the duration of symptoms and the interval before return of the basal temperature to the estrogen level. This is evidence of adequate progesterone secretion. A similar relationship exists between the time factor and excretion of the chorionic gonadotropins.

5. Basal temperatures are helpful in detecting errors in the differential diagnosis of pregnancy.

6. Oral basal temperature curves are presented in two cases of tubal pregnancy. The curve serves no useful purpose in the differential diagnosis of intrauterine and extrauterine gestation.

7. This study supports the opinion that most cases of threatened and spontaneous abortion are not due to a deficiency of estrogen and progesterone.

References

1. Stewart, H. L., Jr.: West. J. Surg. **57**: 192, 1949.
2. Montgomery, T. L., and Stewart, H. L., Jr.: J. M. Soc. New Jersey **39**: 333, 1942.
3. Delfs, E., and Jones, C. E. S.: Obst. & Gynec. Survey **3**: 680, 1948.

Peet, Max M., and Isberg, Emil M.: Some Aspects of Hypertensive Disease of Pregnancy Treated by Splanchnicectomy, Am. J. M. Sc. **217**: 530, 1949.

A study of 452 women in the childbearing age suffering from hypertensive disease and treated by splanchnicectomy is presented. The series covers the years 1934 through 1942, inclusive, and thus it is possible to evaluate fully the results obtained by this operation.

Twenty-eight hypertensive women were treated by splanchnicectomy and subsequently became pregnant. Their average age was 28 years. The average preoperative blood pressure was 208 systolic and 135 diastolic. After operation, but prior to pregnancy, the average blood pressure was 144 systolic and 94 diastolic. Eighteen of these patients began pregnancy with normal blood pressures and seventeen of these eighteen delivered eighteen normal living infants. Of the remaining ten who started their pregnancies above normal, only two delivered living infants at term. Blood pressure readings, taken an average of 2.7 years after delivery, showed that fifteen of the twenty-eight had normal blood pressure readings, in nine there was slight elevation, and in four the blood pressure levels were greater than 170/105.

It seems apparent, therefore, that the once hypertensive woman who, following splanchnicectomy, maintains a normal blood pressure, may be allowed to go through pregnancy with full expectation of delivering a normal living infant and without great danger of vascular damage. Conversely, any hypertensive young woman who desires children should be advised to undergo splanchnicectomy.

Five patients were operated upon during their pregnancies. They had toxemia superimposed on hypertension which existed prior to pregnancy. In two cases the results were excellent, whereas, in the other three cases, the operation exerted no influence on the toxemia.

Of the 452 women studied, hypertension was first noted in 100 of them at the time of pregnancy. While the results in both series were very good, it is interesting to note that the survival rate of the women whose hypertension first appeared during pregnancy was better than that of those whose hypertension was not related to pregnancy. In addition, the fall in blood pressure following splanchnicectomy was better maintained in the pregnant group. The authors compute that in the year 1946 possibly 70,000 of the 3.45 million women who were pregnant now have permanent hypertensive disease which had its onset during pregnancy. They urge that splanchnicectomy be considered for every woman whose blood pressure remains at a hypertensive level for more than one year following childbirth.

HERBERT J. SIMON.

THECA-CELL TUMORS*

With a Report of Twelve New Cases and Observations on the Possible Etiologic Role of Ovarian Stromal Hyperplasia

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THE many case reports and review articles that have appeared since Loeffler and Priesel[1] published the first adequate description of the theca-cell tumor have established this neoplasm as a definite pathologic entity. However, the lines dividing theca-cell tumors from granulosa-cell tumors and ovarian fibromas are not sharply drawn. The histogenesis of the estrogen-producing ovarian neoplasms is still controversial, although there is fairly general agreement that these tumors are not derived from the mature follicular apparatus. The concept of Fischel[2] and others, that ovarian stroma and follicular cells are derived from the ovarian mesenchyme, and that both granulosa- and theca-cell tumors have a common origin in ovarian mesenchyme, has much to commend it. The production of ovarian tumors in mice by irradiation[3, 4] and by intrasplenic ovarian grafts[5, 6] (both of which are techniques which increase pituitary gonadotrophin activity) have in the main lent support to Fischel's concept.

The ovarian stromal cell is apparently capable of differentiating as a theca cell, a granulosa cell, a lutein cell or as a pure connective-tissue element or fibroblast. The stimuli that elicit such differentiation in follicular growth are not well understood. Clearly, pituitary gonadotrophins are important although follicular development may proceed to a certain point in the absence of the pituitary. Hisaw[7] in his fine review has postulated a system of chemical organizers in the follicle; thus, the arrangement of the granulosa of a primordial follicle is under control of the ovum and under some circumstances the granulosa controls the differentiation of surrounding stroma into theca interna. Regardless of the source of the stimuli the potentialities of the ovarian stromal cell for differentiation seem well established.

The evidence, we believe, is also convincing that theca-cell tumors, granulosa-cell tumors, and probably ovarian fibromas all have their origin in the ovarian stromal cell. The morphologic observations to be presented lend further support to this concept. Admixtures of cell types are commonly seen in ovarian neoplasms as a number of authors[3, 8, 9] have indicated. Sharp pathologic distinctions are not always possible, and they may not in fact exist. Granulosa cells and theca cells commonly coexist in the same neoplasm. Fibromas may be histologically similar to theca-cell tumors, and the presence of lipids in the tumor cells is not necessarily associated with significant hormonal activity. There is, furthermore, no reason why some theca-cell tumors might not contain nonfunc-

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tional fibromatous portions or produce estrogens below the threshold of clinical or biologic detection. Many large theca-cell tumors in fact show little evidence of estrogenic activity, while small tumors may produce striking hormonal effects.

The excellent studies of Hertig[10] and of Woll, Hertig, Smith and Johnson[11] on the aging ovary, and especially on the ovarian changes seen in association with endometrial carcinoma, have emphasized the potentialities of the stromal cells in mature ovaries for differentiation. These studies demonstrated the frequency of ovarian stromal hyperplasia in the menopausal period and in patients with endometrial carcinoma. One observation of particular interest in their endometrial carcinoma series was the association of stromal hyperplasia and frank theca-cell tumors in the same patient.

It is the purpose of this paper to present twelve new cases of theca-cell tumor with particular stress on the frequency of hyperplastic changes in the nonneoplastic portions of the ovaries. Ovarian stromal hyperplasia may, we believe, be significant in the etiology of theca-cell tumors.

General

Thecomas are usually unilateral, yellow, firm tumors which may vary in weight from a few milligrams to 7,727 grams (Knight[12]). Unlike the granulosa-cell tumors, they have never been encountered before puberty but like granulosa-cell tumors the great majority occur at or after the menopause. Many of the symptoms arise from the action of estrogens produced in the tumor although other symptoms may result from such complications as twisting of the pedicle, pressure on surrounding viscera, degeneration of the tumor with pain, and ascites or Meigs' syndrome. The tumor is usually benign, only three cases of malignancy having been reported (Loeffler and Priesel,[1] Geist and Gaines[13]). Associated malignancy of the uterus, however, is frequent. Banner and Dockerty[14] found an incidence of 22 per cent in their series of twenty-three cases of theca-cell tumors.

Material

The material for this study was obtained from the Charity Hospital of Louisiana at New Orleans, and from the Touro Infirmary. All ovarian neoplasms diagnosed as fibromas, leiomyomas, sarcomas, or theca-cell tumors from Jan. 1, 1937, through Aug. 31, 1948, were collected and reviewed. At Touro Infirmary there were six acceptable cases of theca-cell tumors, one of which had been reported previously.[15] In two other cases the diagnosis of theca-cell tumor could not be confirmed because the original tissue was not obtainable for special stains, and the histologic evidence available was not adequate to establish a definite diagnosis. Seven cases of theca-cell tumor were collected from the Charity Hospital. Two of these had previously been classified as fibroma. A total of thirteen cases, one of which has previously been published, are therefore presented.

Clinical Observations

The age distribution of the patients with these thirteen tumors follows quite closely that reported in the literature. Fifty-four per cent of the patients were over 50 years of age, the youngest being 18 years old and the oldest 63 years. The average age of this series of patients was 47 years, which is somewhat lower than the average of 52 years in the 70 cases compiled from the literature by Knight.[12] Four of the patients were Negro and nine were white. Six of the ten patients whose obstetrical history was available had had children.

The duration of symptoms varied from three days to ten or twelve years and the presenting complaint was often related to the age of the woman. Seven patients were postmenopausal. Among the seven women who had ceased men-

struating three to eighteen years before the onset of symptoms, four had spontaneous vaginal bleeding and one other had slight bleeding after discontinuing stilbestrol therapy. One postmenopausal patient complained of heaviness in the lower abdomen which probably was explained by the presence of a concomitant large ovarian cyst (14 by 8 by 7 cm.) of undetermined type. In the remaining patient of this group a small theca-cell tumor was an incidental finding at necropsy.

There were six cases in the premenopausal group. Amenorrhea occurred in only two. One of these (Case 5) had a five-month history of amenorrhea, swelling of the breasts and abdomen, and entered the hospital believing she was pregnant. We have classified Case 11 as premenopausal in spite of her history of cessation of menses, because an active corpus luteum was found in the opposite ovary. Two patients (Cases 2 and 12) had menorrhagia for one year prior to surgery. Patient 12 had a large leiomyoma of the uterus which probably accounts for her history of a mass growing in the abdomen for 10 or 12 years. Thus four of the six premenopausal patients had symptoms that could be ascribed to an endocrine dysfunction.

One patient (Case 9) developed the neoplasm either before or during pregnancy since she died one hour after delivery. Massive intra-abdominal hemorrhage caused by rupture of the pedicle of the theca-cell tumor was discovered at autopsy.

All of the tumors presented here were unilateral, four in the right and six in the left ovary. In three cases it could not be determined from the data available whether the tumor was on the left or the right.

The findings in the entire series are summarized in Table I.

Pathologic Observations

The thirteen theca-cell tumors in this series varied in size from 1 cm. in diameter to 22 by 16 by 10 cm. The average diameter was approximately 6 cm. As indicated in previous reports there was no correlation between the degree of hormonal activity as manifested clinically and the size of the tumor. Two tumors less than 2 cm. in diameter showed the greatest hormonal activity as estimated clinically (endometrial hyperplasia, etc.). Both were highly cellular, lipid rich, with little collagen and no hyalinization. In contrast, occasional large tumors with extensive hyalinization showed little clinical evidence of hormonal activity.

The small tumors had no capsules although they were usually sharply demarcated by color and consistency from the surrounding ovarian stroma. A similar absence of encapsulation is seen in small ovarian fibromas. The larger tumors had capsules derived from the adjacent compressed and fibrotic ovarian stroma.

The tumors were generally spherical or ovoid. The consistency was firm and somewhat elastic although softer, more cellular areas were present in some. Cystic degeneration was occasionally present. The cut surface usually revealed interlacing fibrous strands and whorl formation as seen in fibromas. Unlike fibromas however, the characteristic color was yellow, ranging from a pale yellow or tan yellow, to a deep yellow orange or yellow brown. The yellow color was either diffuse or more commonly concentrated in multiple areas, separated by white or gray fibrous trabeculae. Focal areas of calcification were occasionally seen. These observations conform to the generally accepted descriptions of theca-cell tumors.

One tumor was adherent to the posterior surface of the broad ligament, but otherwise neither adhesions nor evidence of invasiveness were noted. One patient (case previously reported[15]) had a typical Meigs' syndrome with ascites and pleural effusion.

TABLE I

CASE	AGE	PARITY	MAIN COMPLAINTS	MENSTRUAL HISTORY	SIZE OF TUMOR	MYOMETRIUM	ENDOMETRIUM	OPPOSITE OVARY	OTHER PATHOLOGIC FINDINGS
1	51	4	Vaginal bleeding 4 months	Menopause at 48 years. Irregular bleeding, 4 months	1 cm. in diameter	Adenomyosis	Polypoid cystic hyperplasia	Stromal hyperplasia, moderate	
2	37	?	Pressure in abdomen, 1 year	Premenopausal. Slight menorrhagia, 1 year	5 by 2 by 1.5 cm.	Leiomyomas	Cystic hyperplasia. Endometrial polyp	Stromal hyperplasia, marked. Thecomatosis. Theca luteinization of follicles	
3	61	0	None. Tumor found on routine examination	Menopause at 50 years. Bleeding after cessation of stilbestrol therapy	6 cm. in diameter	Leiomyomas	Polypoid cystic hyperplasia. Atypical areas, premalignant	Stromal hyperplasia, slight. Fibroma, small	Vaginal smears strongly estrogenic in type. Endometriosis
4	27	0	Pain in lower abdomen, 3 months	Menses regular	12 by 10 by 6 cm.	Normal	Hyperplasia, proliferative	Normal	Died of aleucemic lymphatic leucemia
5	39	1	Thought she was pregnant. Vaginal bleeding	Amenorrhea, 5 months, profuse bleeding, 3 days	10 by 7 by 7 cm.	Normal	Proliferative	Not available. Theca lutein cysts in tumor-bearing ovary	Papillary serous cystadenoma in same ovary as thecoma
6	62	5	Vaginal bleeding, weight loss	Menopause at 52 years. Bleeding once 2 years after menopause. Cyclical bleeding, 4 years	6 by 4.5 by 2 cm.	Hypertrophy	Adenocarcinoma	Not available	

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7	52	4	Vaginal bleeding, weight loss 3 months	Irregular bleeding, 3 months	6 cm. in diameter	Hypertrophy. Leiomyomas	Polypoid cystic hyperplasia	Stromal hyperplasia, marked. Thecomatosis, theca lutein cyst	Carcinoma in situ, cervix
8	52	?	Admitted in coma	Not known	1 cm. in diameter	Adenomyosis	Stromal edema, sparse glands. Polyp		Died of vascular cerebral accident
9	18	1		Patient pregnant. No menstrual data	22 by 16 by 10 cm. 1,900 grams	Physiologic hypertrophy of pregnancy	Postpartal	Regressing corpus luteum	Died 1 hour postpartum. Intra-abdominal hemorrhage from tumor pedicle
10	63	12	Vaginal bleeding 1 year	Menopause at 46 years. Irregular bleeding, 1 year	1.5 cm. in diameter	Adenomyosis	Polypoid cystic hyperplasia	Stromal hyperplasia, moderate	
11*	44	0	Swelling of abdomen, backaches, 2 weeks	Premenopausal. Amenorrhea, 1 year	12 by 7 by 7 cm.	Leiomyoma	Proliferative	Cystic corpus luteum. Stromal hyperplasia, moderate	Meigs' syndrome
12	49	0	Mass in abdomen, 10 to 12 years	Premenopausal. Slight menorrhagia	240 grams	Leiomyomas	Proliferative. Polyps with hyperplasia	Fibroma. Stromal hyperplasia, moderate	
13	63	?	Heaviness in abdomen, 6 months	Regular until menopause at 45 years. No bleeding since	6 by 5 by 2 cm.	Leiomyoma	Atrophic, cystic	Stromal hyperplasia, marked	

*Previously reported.[15]

One patient had a papillary serous cystadenoma in the same ovary that contained the theca-cell tumor and in another case a large cyst in the tumor-bearing ovary was not classified histologically. One of the three patients who came to autopsy died of aleucemic lymphatic leucemia two years after surgical excision of the theca-cell tumor. Another died of massive postpartum hemorrhage from the pedicle of the tumor. A theca-cell tumor was an incidental finding in the third autopsy, the cause of death being a cerebral vascular accident.

Microscopic Observations.—The histologic features of the tumors paralleled closely the established descriptions in the literature. The tissues were studied with hematoxylin and eosin, Masson trichrome stain, and the Wilder silver impregnation technique for reticulum. Sudan III stains of frozen sections revealed variable quantities of intra- and extra-cellular lipid finely dispersed, with scattered foci containing large masses of sudanophilic substance.

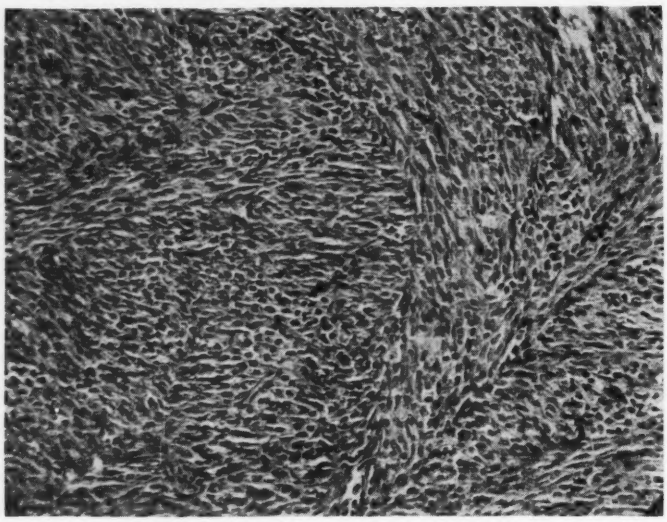

Fig. 1 (Case 1).—Photomicrograph of small theca-cell tumor showing marked cellularity, plump cells, and luteinlike cells.

The tumors varied from highly cellular forms containing plump spindle cells, well-vacuolated cytoplasm, and clusters of ovoid luteinlike cells to more fibrous forms in which the predominant cell was an elongate spindle cell. The former, while containing a rich meshwork of argentophil reticulum encasing virtually every cell, had few condensations of collagen. Collagenous strands were more prominent in the latter. Hyalinized plaques and bands were numerous in the majority of tumors, and were variable in distribution. Portions of some tumors were converted into broad hyaline masses containing only a few compressed and atrophic theca cells.

A number of investigators[16, 17, 18] have used silver impregnation to distinguish theca cells from granulosa cells in neoplasms. In normal follicles an argentophil reticulum surrounds the individual cells in the theca-cell zone. In the granulosa no such reticulum is present but the granulosa cells contain argentophil granules. These criteria have been used to differentiate the cells in tumors, but the technique is probably not as specific as some have claimed. This is exemplified by one tumor in which granulosa and theca cells appeared to be about equally represented. In selected areas stained with the Wilder reticulum stain the distinction between cell types was sharp, granulosa cells showing abundant reticulum but with no silver impregnation of the cells. In other areas of

the same section the staining reactions were ambiguous and no definite decision as to cell type could be made. We have omitted from our series tumors containing such admixtures of cell types, including only those in which the preponderant cell was thecal.

Uterine Changes.—The myometrium contained leiomyomas in six of the thirteen cases. Two patients had myohypertrophy and three had adenomyosis. The percentage of cases with proliferative hyperplasia of the endometrium was high compared to that of other series of thecomas. Seven of the thirteen had endometrial hyperplasia, usually cystic and polypoid in character. Endometrial polyps were present in three others.

Fig. 2.

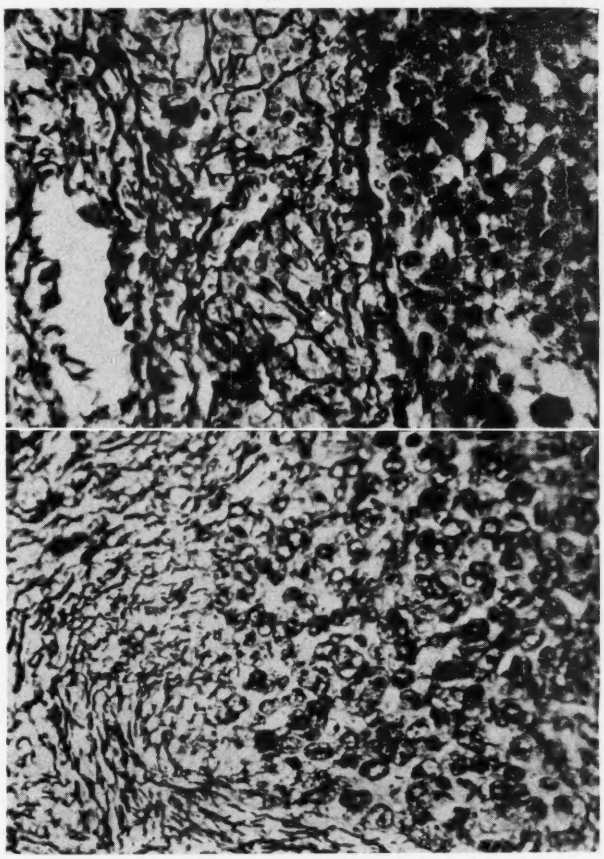

Fig. 3.

Fig. 2.—Photomicrograph of border of ovarian follicle from normal adult woman, showing theca externa (left); theca interna, luteinized (middle); and granulosa (right). The theca cells have silver-positive reticulum fibrils about each cell but show no affinity for silver. The granulosa cells lack any reticulum but show silver staining particularly in the nuclei. Wilder stain for reticulum.

Fig. 3.—For comparison, a mixed theca- and granulosa-cell tumor showing similar staining characteristics as Fig. 2. Theca cells on left, granulosa cells on right. Other sections of the tumor failed to show such clear-cut distinctions. From a case not included in the series. Wilder stain for reticulum.

Adenocarcinoma of the endometrium was present in one patient 62 years old. Another 61-year-old patient with cystic hyperplasia of the endometrium showed premalignant glandular changes in several polyps. One patient of 52 years had cervical carcinoma in situ within the endocervical canal.

Endometriosis involving the tubes and broad ligament was present in one patient even though she was eleven years past the menopause.

Stromal Hyperplasia and Other Ovarian Changes.—The changes noted in ovarian tissue outside of the neoplasms were of particular interest. The ovarian stromal cells showed histologic evidence of significant hyperplasia in all patients in the fourth decade and beyond, in whom tissue was available for study (Patients 1, 2, 3, 7, 10, 11, 12, 13). The frequency and degree of stromal activity suggested that its association with theca-cell tumors was not fortuitous.

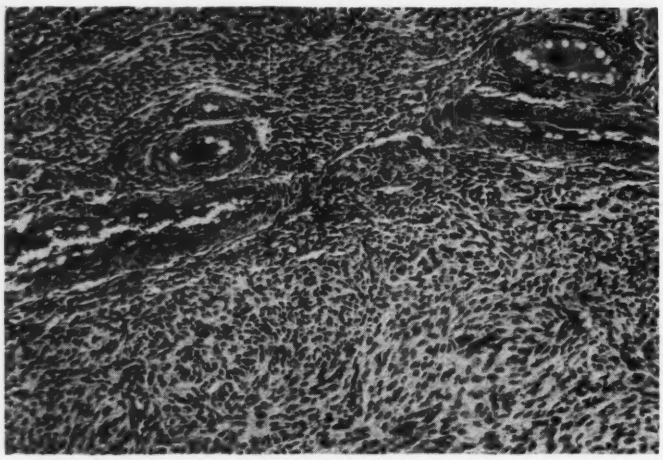

Fig. 4 (Case 10).—Photomicrograph of a small cellular theca-cell tumor showing lack of capsule and gradual transition from ovarian stroma (above) to tumor (below).

The sequences of ovarian stromal hyperplasia as described by Woll and associates[11] in admirable detail are worth summarizing since they bear closely on the problem of theca-cell tumors. The ovaries with stromal hyperplasia had a deeply staining cortex with spherical or scalloped nodulation. The pattern was reminiscent of miliary leiomyomas seen in the myometrium. Whorls and fascicles were more prominent than in normal ovarian cortex. Collagen was scarce, capillaries, prominent, and the nuclei were oval and blunt, rather than spindle shaped. In a more advanced, though less common form, scattered stromal cells became frankly epithelioid, with lipid-laden cytoplasm and round nuclei. This stage was designated as thecomatosis. Stromal hyperplasia was uncommon before the fourth decade, reached its height in the sixth decade and tended to subside thereafter. It was significantly more frequent in patients with endometrial carcinoma than in normal patients and was morphologically more vigorous, persisting into advanced senility. All patients with theca-cell tumors in their series also showed stromal hyperplasia of some degree in the opposite ovary.

In our series of theca-cell tumors the opposite ovary was available for study in ten of the thirteen patients. Two patients (aged 18 and 27 years) were in the age group where stromal hyperplasia is not ordinarily manifest. The remaining eight fell in the fourth decade, or beyond. A significant degree of ovarian stromal hyperplasia was present in all eight. In one, the process was slight; in four, moderate; and in three, stromal hyperplasia was marked. Two of the latter three also showed thecomatosis and focal areas of luteinization of the stroma, and one, aged 52 years, and according to her history six years past the menopause, had a small theca lutein cyst in addition to focal areas of luteinlike cells in the stroma. A 39-year-old patient, whose opposite ovary was not available for study, had recognizable but compressed and fibrotic ovarian tissue at

the periphery of the theca-cell tumor. Although the stromal changes could not be properly evaluated because of the distortion due to the tumor, there were two small theca lutein cysts and foci of lutein cells in the ovarian stroma. Two patients aged 49 and 63 years had fibromas of the opposite ovary in addition to stromal hyperplasia.

Fig. 5.

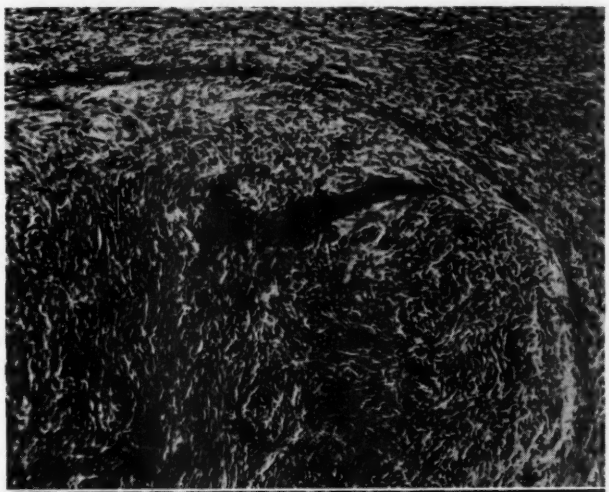

Fig. 6.

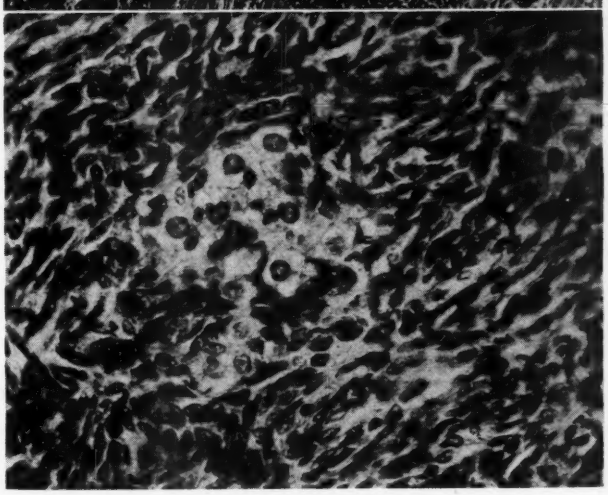

Fig. 5 (Case 7).—Opposite ovary from theca-cell tumor showing ovarian stromal hyperplasia with characteristic nodular formation.

Fig. 6 (Case 7).—Higher magnification of same ovary as in Fig. 5 showing characteristics of hyperplastic ovarian stromal cells, and luteinization of stromal cells. Patient six years past menopause.

These findings indicate a diffuse activity in the ovarian stroma and suggest that stromal hyperplasia is the soil in which theca-cell tumors are likely to develop. Furthermore, there is a definite similarity in the structure of the small nodules of stromal hyperplasia and the small theca-cell tumors. The small tumors lack a capsule and at points their transition from ovarian stroma is not sharp. One also sees in both an accentuation of whorl formation, cells with a more oval, less elongate nucleus, than in the resting stromal cell, and occasional transformations of stromal cells to luteinlike cells. In two instances the cellular

pattern of thecoma was remarkably similar to the hyperplastic ovarian stroma throughout the cortex of the opposite ovary, where no tumor was present (Figs. 7 and 8).

Fig. 7.

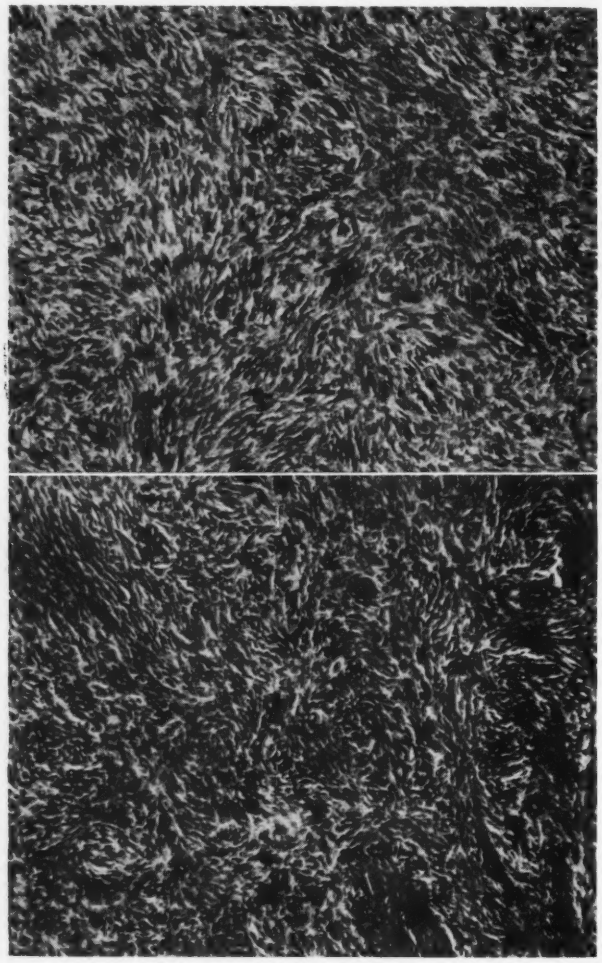

Fig. 8.

Fig. 7 (Case 13).—Photomicrograph of theca-cell tumor.

Fig. 8 (Case 13).—Compare with Fig. 7. Opposite ovary of same patient showing stromal hyperplasia and resemblance to theca-cell tumor.

Perhaps the two instances of associated ovarian fibromas are also reflections of the same diffuse stimulation of the ovaries. Other authors[19, 20] have noted cases of theca-cell tumors with accompanying ovarian fibromas. Dockerty and Masson,[21] in their study of ovarian fibromas, have described examples of diffuse, bilateral fibromatosis of the ovaries—a process which may be analogous to thecomatosis.

Discussion

The series of theca-cell tumors here presented conforms generally both clinically and pathologically to the previously published cases. The notable exception is the finding of histologic evidence of ovarian stromal hyperplasia in the nonneoplastic ovarian tissue. The morphologic evidence of ovarian

stromal activity outside of the tumors, the apparent histologic transitions from stromal hyperplasia, to diffuse thecomatosis, and then to theca-cell tumor, suggest that the theca-cell tumor tends to emerge against a background of diffuse ovarian stimulation. There is furthermore a fairly good correspondence in the age incidence of ovarian stromal hyperplasia, theca-cell tumors and ovarian fibromas. The peak incidence of all three is the sixth decade.

The ovarian stroma, as Woll and co-workers[11] have pointed out, may differentiate into cells of granulosa, theca interna, corpus luteum, etc., in the normal sequences of follicle maturation. In senescence, with diminution or absence of ova, this process may be repeated diffusely and imperfectly in the ovarian cortex, leading to stromal hyperplasia. There is, furthermore, good evidence that the specific ovarian stroma is capable of elaborating estrogen apart from the follicle. Animals in which the follicular apparatus has been damaged or destroyed by x-ray may continue to elaborate estrogen from the ovary, as evidenced by the persistence of estrous smears which disappear only following ovariectomy.[22]

Although little is known of the source of the stimuli which produce ovarian stromal hyperplasia, it is likely that the pituitary plays a role. Woll and associates[11] on theoretical grounds have suggested that the luteinizing hormone is most important. Three of our patients had some theca luteinization of follicles. Of some interest too was the single case in which urinary pituitary gonadotrophin was measured. Despite the fact that this postmenopausal patient had definite evidence of excessive estrogenic activity (cystic hyperplasia of endometrium, endometriosis, strongly estrogenic vaginal smears) which might be expected to suppress pituitary activity, her pituitary gonadotrophin was markedly elevated.

Although we are in full agreement with the morphological observations of Woll and associates,[11] we cannot accept some of their interpretations of the significance of stromal hyperplasia. These authors have theorized that the high incidence of ovarian stromal hyperplasia in patients with endometrial carcinoma is the result of tissue breakdown, i.e., protein catabolism, in the carcinoma, the catabolites stimulating the pituitary to secrete and release luteinizing hormone which produces changes in the ovarian stroma. This concept is based on the experimental work of Smith and Smith,[23, 24] who used fresh menstrual discharge to stimulate the production of luteinizing hormone, as well as on clinical observations by the same authors. If this interpretation is correct, the endometrial carcinoma precedes and is responsible for the ovarian changes via pituitary stimulation. The ovarian changes then would be incidental findings unrelated to the pathogenesis of endometrial carcinoma. And if the theca-cell tumor represents one of the end stages or results of stromal hyperplasia (as we, and apparently Woll and his co-workers believe it may) then the significant association of endometrial carcinoma and theca-cell tumors must be explained by assuming that the endometrial carcinoma precedes and predisposes to thecoma formation. This is a concept difficult to accept. Clinical histories and pathologic studies of such cases strongly suggest that the endometrial carcinomas *follow* the theca cell (or other estrogen-producing) tumors rather than precede them. In presenting their thesis, Woll and associates[11] minimize the role of estrogen as an etiological factor in the production of endometrial carcinoma. Without engaging in further discussion of this much belabored subject we believe that the evidence, experimental and clinical, suggests very strongly that estrogens play an important (though not a lone) role in the pathogenesis of endometrial carcinoma.

The high correlation between stromal hyperplasia and theca-cell tumors as indicated by the observations of Woll[11] as well as by the present authors might conceivably be explained as the result of estrogen produced by the tumors and acting on the remaining ovarian tissue, perhaps through the pituitary. This is

a less likely alternative, we believe, since transition forms from nodular stromal hyperplasia to theca-cell tumor strongly suggest that the latter develops out of the former. Woll points out that in several instances of thecomatosis (the advanced form of stromal hyperplasia) the diagnosis of theca-cell tumor was hard to avoid.

Several other findings are worthy of comment. Some authors have noted an absence of corpora lutea in association with theca-cell tumors, attributing the estrogenic effects of the tumor to the unopposed action of the hormone, rather than to unusually high estrogen production. Since so many of the tumors occur after the menopause the absence of corpora lutea is not surprising. One of our patients did have a well-formed corpus luteum, vascularized and apparently active. The endometrium, surprisingly, was proliferative rather than secretory. In the case of the theca-cell tumor with pregnancy, a regressed corpus luteum was also present, as would be expected.

Pregnancy with a theca-cell tumor is rare. We are aware of only one other reported case.[25] The age incidence of the neoplasms and their excessive production of estrogen would of course reduce the likelihood of pregnancy. Since the theca-cell tumor with pregnancy was the largest neoplasm in our series it is probable that it existed before pregnancy although one might speculate that chorionic gonadotrophin might in part account for its size and cellularity. If the tumor existed before pregnancy it is apparent that its estrogen production was insufficient to cause infertility. The fatal hemorrhage from the tumor pedicle with parturition was a unique and unfortunate accident.

Extrauterine endometriosis in one patient eleven years past the menopause again emphasizes the endocrine function of the tumor. Occasional examples of endometriosis with granulosa-cell tumors have also been recorded.[26] Estrogen produced by the tumor clearly led to many of the symptoms in the patient who erroneously thought herself pregnant.

The finding of one frank adenocarcinoma of the fundus, one example of atypical and probably premalignant endometrial hyperplasia, and one carcinoma in situ in the cervix exemplifies the potential menace of these tumors, as stressed particularly by Banner and Dockerty.[14] This danger is an important consideration in determining treatment, especially in the older age groups.

One instance of death due to aleucemic lymphatic leucemia two years following removal of a theca-cell tumor is recorded. Reviewing the clinical history, it is altogether likely that the leucemia existed undiagnosed at the time of the operation and perhaps contributed to the symptoms. Dr. William H. Harris, Jr.,[27] has recently studied a case of malignant granulosa-cell tumor which at autopsy also revealed a previously undiagnosed aleucemic leucemia. We are indebted to him for permission to refer to his case. We are not aware of other reports of leucemia in association with estrogen-producing tumors. Since Gardner[28] has established the leucemogenic action of estrogens in certain strains of mice, we cannot help speculating on the possible relationship between the estrogen-producing tumor and the leucemia in these two cases.

Summary

1. Clinical and pathologic data on twelve additional cases of theca-cell tumor of the ovary are presented.

2. Adenocarcinoma of the endometrium was present in one, atypical hyperplasia of the endometrium, premalignant in character in another, and carcinoma in situ of the cervix in a third.

3. Unusual clinical findings included a case of pregnancy with death at parturition due to rupture and hemorrhage from the tumor pedicle; a case in

which the symptomatology simulated pregnancy; a case of endometriosis in a woman eleven years postmenopausal; and an instance of associated aleucemic lymphatic leucemia.

4. Examination of the nonneoplastic ovarian tissue revealed a significant degree of ovarian stromal hyperplasia in all eight patients in the fourth decade and beyond, in whom tissue was available for study.

5. The high incidence of ovarian stromal hyperplasia and other evidences of stromal activity, in the nonneoplastic ovarian tissue suggests that the theca-cell tumor may develop against a background of diffuse ovarian stromal stimulation.

6. The age incidence of theca-cell tumors parallels that of ovarian stromal hyperplasia and ovarian fibromas.

7. Urinary gonadotrophin was elevated in one postmenopausal patient with clinical evidence of estrogenic activity of the theca-cell tumor.

References

1. Loeffler, E., and Priesel, A.: Beitr. z. path. Anat. u. z. allg. Path. **90**: 199, 1932.
2. Fischel, A.: Ztschr. f. d. ges. Anat. (Abt. 1) **92**: 34, 1930.
3. Furth, J., and Butterworth, J. S.: Am. J. Cancer **28**: 66, 1936.
4. Geist, S. H., Gaines, J. A., and Pollack, A. D.: Am. J. Obst. & Gynec. **38**: 786, 1939.
5. Biskind, M. S., and Biskind, G. R.: Proc. Soc. Exper. Biol. & Med. **55**: 176, 1944.
6. Li, H. L., and Gardner, W. U.: Cancer Research **7**: 549, 1947.
7. Hisaw, F. L.: Physiol. Rev. **27**: 95, 1947.
8. Traut, H. F., and Marchetti, A. A.: Surg., Gynec. & Obst. **70**: 632, 1940.
9. Novak, E.: Endocrinology **30**: 953, 1942.
10. Hertig, A. T.: J. Clin. Endocrinol. **4**: 581, 1944.
11. Woll, E., Hertig, A. T., Smith, G. Van S., and Johnson, L.: Am. J. Obst. & Gynec. **56**: 617, 1948.
12. Knight, W. R.: Am. J. Obst. & Gynec. **56**: 311, 1948.
13. Geist, S. H., and Gaines, J. A.: Am. J. Obst. & Gynec. **35**: 39, 1938.
14. Banner, E. A., and Dockerty, M. B.: Surg., Gynec. & Obst. **81**: 234, 1945.
15. Mendel, E. B., and Tyrone, C.: Am. J. Obst. & Gynec. **48**: 271, 1944.
16. Traut, H. F., Kuder, A., and Cadden, J. F.: Am. J. Obst. & Gynec. **38**: 798, 1939.
17. Henderson, D. N.: Am. J. Obst. & Gynec. **43**: 194, 1942.
18. Wolfe, S. A., and Neigus, I.: Am. J. Obst. & Gynec. **42**: 218, 1941.
19. Patterson, J. H., and McCullagh, W. M. H.: J. Obst. and Gynaec. Brit. Emp. **43**: 1186, 1936.
20. McGoldrick, J. L., and Lapp, W. A.: Am. J. Obst. & Gynec. **48**: 409, 1944.
21. Dockerty, M. B., and Masson, J. C.: Am. J. Obst. & Gynec. **47**: 741, 1944.
22. Brambell, F. W. R., Parkes, A. S., and Fielding, U.: Proc. Roy. Soc. London **101**: 29, 1927.
23. Smith, O. W., and Smith, G. Van S.: J. Clin. Endocrinol. **6**: 483, 1946.
24. Smith, O. W.: Am. J. Obst. & Gynec. **54**: 201, 1947.
25. Kusuda, S.: Arch. f. Gynäk. **124**: 269, 1925. Cited by Selye, H. Encyclopedia of Endocrinology, Montreal, 1946, Richardson, Bond and Wright, section IV, vol. VII.
26. Novak, E., and Brawner, J. N.: Tr. Am. Gynec. Soc. **59**: 223, 1934.
27. Harris, W., Jr.: Personal communication.
28. Gardner, W. U., Dougherty, T. F., and Williams, W. L.: Cancer Research **4**: 73, 1944.

A TWENTY-YEAR STATISTICAL REVIEW OF 454 CONSECUTIVE CESAREAN SECTIONS*

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THIS cesarean section study was compiled from the obstetrical records of St. Joseph Hospital, a two hundred sixty bed general hospital, and covered the period from 1928 to 1947, inclusive. The survey was then divided into two ten-year periods; 1928 to 1937 and 1938 to 1947, to compare the results statistically and determine what progress, if any, has been made in the last decade. In 1938 the Chicago Board of Health instituted rules and regulations for the management of obstetrical departments in the various hospitals in this city. With reference to cesarean section it was necessary for the attending physician to call consultation prior to this operative procedure unless he was approved as a specialist in obstetrics. Since the adoption of this program all cesarean indications are reviewed and all maternal deaths are investigated. Also the 1938 to 1947 years marked the advent of chemotherapy, antibiotics, plasma, and bank blood; sulfanilamide was first introduced commercially in January, 1938, and penicillin was made available for civilian use on March 15, 1945. Plasma and blood have been readily available in this hospital only during the last five years. We were interested in learning the effect of obstetrical control and modern aids regarding the management of the cesarean problem.

TABLE I. YEARLY INCIDENCE OF CESAREAN SECTION

YEAR	NO. OF DELIVERIES	NO. OF SECTIONS	INCIDENCE OF SECTIONS (PER CENT)
1928	650	13	2.00
1929	624	21	3.36
1930	651	22	3.37
1931	547	16	2.90
1932	491	19	3.90
1933	411	14	3.40
1934	476	19	3.99
1935	465	29	6.20
1936	390	19	4.87
1937	592	16	2.70
1938	654	25	3.82
1939	698	16	2.29
1940	840	22	2.61
1941	1055	20	1.89
1942	1331	29	2.17
1943	1185	27	2.28
1944	1101	20	1.80
1945	1069	27	1.54
1946	1448	28	1.93
1947	1552	52	3.30

*Presented before the Chicago Gynecological Society, Jan. 21, 1949.

In the twenty-year period there were 16,170 deliveries which included 454 cesarean sections, an incidence of 2.80 per cent for all deliveries. The 1928 to 1937 group comprised 5,306 deliveries with 188 cesareans for a section rate of 3.54 per cent, and in the 1938 to 1947 period there were 10,864 births with 266 sections for an incidence of 2.44 per cent. It is obvious that the total number of deliveries during the last decade doubled that of the first ten years but yet the incidence of cesarean section was reduced by 1 per cent.

The incidence of cesarean section, as reported by various authors throughout the country, during the last ten years varies from 1.50 per cent to 8.28 per cent as noted in Table X. The average incidence in the aforementioned table is 3.53 per cent which is comparable to our 3.54 per cent for our first ten-year group while our second ten-year period reveals an incidence of 2.44 per cent, considerably lower than the general average incidence.

TABLE II. AGE GROUPS

AGE	1928-1937	1938-1947	1928-1947
15-19 years	8	9	17
20-24 years	42	54	96
25-29 years	35	70	105
30-34 years	43	63	106
35-39 years	45	50	95
40 years plus	15	20	35
	188	266	454

Table II indicates there were seventeen cesarean sections in the youngest age group. Ten of these were performed for toxemia; these patients were all primiparas, with a very severe and fulminating toxemia, not responding to conservative management and with a long, thick cervix. Two were operated upon for placenta previa centralis, one for abruptio placentae and four for cephalopelvic disproportion.

TABLE III. TYPES OF CESAREAN SECTION

	1928-1937		1938-1947		1928-1947	
	NO. SECTIONS	PER CENT	NO. SECTIONS	PER CENT	NO. SECTIONS	PER CENT
Classical	126	67.5	65	24.5	191	42.0
Low cervical	61	32.0	189	71.0	250	55.0
Porro	1	0.5	12	4.5	13	3.0
	188	100.0	266	100.0	454	100.0

It is our opinion that the low cervical cesarean section is the preferable type of procedure; whether the incision in the lower uterine segment is longitudinal or transverse is immaterial. Ninety per cent of the cesarean sections in the first ten-year period were performed by general surgeons while in the second decade eighty-five per cent were performed by specialists in obstetrics. Forty of the sixty-five classical types in the second series were done by general surgeons while the balance, twenty-five, were performed by obstetricians. Table III indicates the trend toward the low-flap transperitoneal operation in the second ten-year period. The Porro operation was utilized twelve times in the second series compared to once in the first group. There were no extraperitoneal operations performed in this hospital that can be included in this survey.

The incidence of 2.80 per cent for cesarean hysterectomy in this twenty-year analysis compares favorably with the average incidence indicated in Table IV. It is our policy to do this operation in the grossly pathologic uterus, particularly that associated with multiple fibroids, and also in those uteri which present

uncontrollable bleeding at the time of surgery and occasionally for severe intrapartum infection. Dieckmann[2] states that two-thirds of the cases of puerperal infection are due to bacteria that are not amenable to antibiotics or the sulfonamide group of drugs and that cesarean hysterectomy in the treatment of the infected uterus should have a mortality of less than 2 per cent. There were no maternal deaths following this operation in this series.

TABLE IV. INCIDENCE OF CESAREAN HYSTERECTOMY

YEAR REPORTED	YEARS SURVEYED	PLACE	AUTHOR	NO. OF DELIVERIES	CESAREAN HYSTERECTOMY	INCIDENCE	MATERNAL MORTALITY PER CENT
1949	1928-1947	St. Joseph	. . . .	16,170	13	2.80	0
1948	1931-1947	Chicago Lying-in	Dieckmann[2]	46,949	153	6.30	0.65
1946	1933-1945	Michael Reese	Reis[1]	23,214	54	4.50	0
1945	1934-1943	Boston Lying-in	Irving[3]	45,218	46	2.40	4.30
1944	1932-1942	Bronx Hosp.	Rosensohn[7]	20,763	9	1.80	22.20
1943	1932-1942	Philadelphia Lying-In	Mohler[6]	22,754	34	2.57	11.70
1943	1937-1942	Bellevue	Studdiford[9]	7,589	10	6.10	0
1942	1937-1941	State of Massachusetts	DeNormandie[4]	333,731	47	1.30	9.50
1940	1927-1936	City of New Orleans	King[8]	92,936	39	3.50	10.30
1938	1930-1937	Cedars of Lebanon	Lazard[5]	6,891	39	6.80	2.56

TABLE V. INDICATIONS FOR CESAREAN SECTIONS

	1928-1947	INCIDENCE	1928-1937	INCIDENCE	1938-1947	INCIDENCE
Disproportion	136	29.90	60	30.00	76	28.50
Repeat section	131	28.80	51	27.00	80	30.00
Toxemia	67	14.70	27	14.30	40	15.00
Placenta previa	42	9.25	17	9.00	25	9.30
Abruptio placentae	22	4.80	7	3.70	15	5.60
Previous gynec. surgery	15	3.30	5	2.60	10	3.70
Uterine inertia	11	2.40	6	3.10	5	1.80
Elderly primipara	9	1.90	3	1.50	6	2.20
Contraction ring	5	1.10	5	2.60	0	0
Habitual death of fetus	3	.66	1	.50	2	.75
Uterus didelphus	2	.44	0	0	2	.75
Ruptured uterus	3	.66	0	0	3	1.12
Previous pubiotomy	1	.22	1	.50	0	0
Medical indications	6	1.32	5	2.66	1	.37
Cardiac disease 3						
Aplastic anemia 1						
Thyrotoxicosis 1						
Active tuberculosis 1						

Cephalopelvic Disproportion.—

This comprises about one-third of the total indications for performing cesarean section in this series. Its incidence throughout each ten-year period remained rather constant. All patients with a questionable or borderline disproportion, as demonstrated by the Hillis Method of Impression or by x-ray pelvimetry, are given an adequate test of labor. This, we define, as pains, five minutes or less in frequency for twelve to twenty hours, with contractions lasting between thirty and sixty seconds in duration. If the bag of waters has been ruptured twenty-four hours or longer the case must be carefully evaluated for there is an acute rise in the bacterial count of these uteri after this period.

X-ray pelvimetry is being utilized more frequently in the primipara and with the latest improvements in technique it is demonstrating the adequacy of the questionable pelvis.

Previous Cesarean Section.—

This indication also accounts for about one-third of the operations and this figure has not varied in the two decades. If a patient has had a cesarean section with her primiparous delivery we believe in the repeat cesarean section, unless she arrives in the hospital in active labor and with the head well below the spines, the cervix soft and dilating rapidly, and with no particular morbidity with the first operation.

Toxemia of Pregnancy.—

The toxemia incidence of 14.7 per cent was in primiparous patients whose toxemia did not respond to conservative management; in this group there were some cases with combined indications, such as questionable pelvic disproportion, elderly primipara, breech presentation, etc. However, the toxemia was severe enough to make it the primary indication and hence we have included these under our toxemia indications. The presence of combined indications with toxemia, not responding to treatment, certainly aids the obstetrician in making his decision for abdominal delivery. In pre-eclampsia with a decreasing proteinuria, falling blood pressure, and increasing urinary output, we will wait for days for the cervix to ripen so that delivery may be effected through the vaginal route. A very severe primiparous toxemia, not responding to conservative management, has a lessened infant and maternal mortality when subjected to abdominal section.

Placenta Previa.—

Placenta previo centralis and partial placenta previa covering 50 per cent or more of the cervical os are usually treated with cesarean section; this group comprises about 25 per cent of all placenta previa cases. We routinely employ the low-flap operation in these cases and do not concur with some authors who prefer the classical operation in order to avoid the placental site. We have been well satisfied in the multiparous patient, and in most primiparas with marginal placenta previa, with a ripe or nearly ripe cervix, to rupture the bag of waters, administer small doses of Pitocin and, if necessary, apply a Willett forceps to the fetal head. In those cases of extremely marked vaginal hemorrhage, at or near term, we take the patient directly to the operating room rather than the delivery room. With crossmatched blood available, a sterile vaginal examination is performed after the patient has been prepared for abdominal delivery. Patients in the last trimester of pregnancy with vaginal bleeding are not allowed any type of examination, rectal or vaginal, until blood has been cross-matched. It has been our policy in this hospital for all men to submit a prenatal list from six to eight weeks before term with the Rh factor and blood type on every obstetrical case. Placenta previa was the indication for cesarean section in about 9 per cent of our cases in this study.

Abruptio Placentae.—

Premature separation of the placenta in the multipara is usually treated with rupture of the bag of waters, possibly the administration of small doses of Pitocin, and careful observation, and always having from 500 to 1,500 c.c. of cross-matched blood in the delivery room. Ablatio placentae in the primipara, and in some multiparas, demands more careful consideration; the treatment is dependent upon the condition of the cervix, the severity of the abruptio condition, the presentation, and the obstetric adequacy of the maternal pelvis. In our series abruptio placentae was the indication for about 5 per cent of the cesarean sections.

TABLE VI. CESAREAN SECTION MORBIDITY

	1928-1937			1938-1947			1928-1947		
	TOTAL	MORBID	PER CENT	TOTAL	MORBID	PER CENT	TOTAL	MORBID	PER CENT
Classical	126	56	44.50	65	27	41.50	191	83	43.40
Low cervical	61	27	44.50	189	60	31.00	250	87	34.80
Porro	1	0	0	12	3	25.00	13	3	23.00

Our morbidity statistics are based on the classification of the American Maternal Welfare Committee: a temperature of 100.4° F. or higher on any two days of the postpartum period exclusive of the first twenty-four hours. The 13 per cent decrease of morbidity in the low cervical cesarean sections during the second period was probably aided by antibiotics, sulfonamides, and blood replacement. An analysis of our detailed morbidity chart reveals that the elective cesarean section has a much lower incidence of morbidity than one performed after labor has ensued or the bag of waters ruptured. All cases in labor twelve or more hours with the bag of waters ruptured, or with a questionable pelvis, abnormal presentation, or uterine inertia are given prophylactic antibiotics and frequently sulfonamide therapy. Early ambulation has been an aid in lowering the morbidity and also in decreasing the incidence of postoperative complications; our patients routinely arise from bed on the evening of the first postoperative day. Douglas and Landesman[10] state there is only a moderate decrease in wound infections after prophylactic therapy but the severity of the wound infection is markedly reduced. We have noted a 30 per cent decrease in incidence of wound infections in the second ten-year period where we have utilized prophylactic agents. We agree with the authors that the severity of the wound infection is very definitely reduced with these measures.

TABLE VII. CESAREAN SECTION MORTALITY

	1928-1937			1938-1947			1928-1947		
	TOTAL	DEATHS	PER CENT	TOTAL	DEATHS	PER CENT	TOTAL	DEATHS	PER CENT
Classical	126	7	5.50	65	3	4.60	191	10	5.23
Low cervical	61	4	6.50	189	1	0.50	250	5	2.00
Porro	1	0	0	12	0	0	13	0	0
	188	11		266	4		454	15	

The gross maternal cesarean section mortality for the twenty-year period is rather high. There were fifteen deaths, an incidence of 3.30 per cent. Eleven deaths, or 5.70 per cent, occurred in the first decade while in the last ten-year series there were four deaths for an incidence of 1.50 per cent. Thus, there has been a reduction in maternal cesarean section mortality of 4.20 per cent in the second ten-year period.

TABLE VIII. MATERNAL DEATHS, 1928 TO 1937

YEAR	OBSTETRICAL INDICATION	CAUSE OF DEATH
1928	Disproportion	Peritonitis
1929	Disproportion	Peritonitis
1929	Disproportion	Peritonitis
1930	Eclampsia	Renal anuria
1930	Thyrotoxicosis	Cardiac death
1935	Disproportion	Peritonitis
1935	Toxemia	Acute yellow atrophy of liver
1935	Disproportion	Peritonitis
1936	Abruptio placentae	Hemorrhage
1937	Placenta previa	Hemorrhage
1937	Disproportion	Peritonitis

TABLE IX. MATERNAL DEATHS, 1938 TO 1947

YEAR	OBSTETRICAL INDICATION	CAUSE OF DEATH
1940	Toxemia	Pulmonary embolism
1941	Toxemia	Renal anuria
1942	Abruptio placentae	Hemorrhage
1947	Aplastic anemia (fetal salvage)	Aplastic anemia

Of the eleven deaths in the first ten-year period, six were due directly to infection while there were no deaths attributable to peritonitis in the second ten years. This was achieved by obstetrical control, by encouraging the low cervical section, by utilizing the cesarean hysterectomy when indicated; and finally, with the aid of antibiotics, chemotherapy, and the frequent use of blood transfusions. There were two deaths due to hemorrhage in the first period and one in the second ten years, all three of which are classified as preventable and all of which occurred before the advent of the blood bank. There were three deaths due to toxemia, two of which occurred in the first ten years. One cesarean death due to cardiac failure occurred in the first ten years and a heart condition was the indication for three cesarean operations during this period. There were no sections performed in the second ten-year group for cardiac disease. In the second decade pulmonary embolism accounted for one death and another occurred following a cesarean on a moribund patient with aplastic anemia for fetal salvage.

The over-all maternal mortality for the 16,170 deliveries in the twenty-year period was 0.26 per cent; in the first ten years the mortality rate was 0.45 per cent, while the second ten-year period reduced the incidence to 0.17 per cent. This is the same incidence presented by Cosgrove[11] at the Margaret Hague Maternity Hospital for 67,959 deliveries for the years 1938 to 1947, inclusive; and the exact figure given by Davis[12] of the Chicago Lying-in Hospital for 39,719 deliveries for the years 1931 to 1945.

TABLE X. CESAREAN SECTION MORTALITY STATISTICS

YEAR REPORTED	YEARS SURVEYED	SOURCE	AUTHOR	NO. OF DELIVERIES	SECTIONS	INCIDENCE	MATERNAL MORTALITY
1949	1928-1937	St. Joseph	. . . . .	5,306	188	3.54	5.70
1949	1938-1947	St. Joseph	. . . . .	10,864	266	2.44	1.50
1949	1928-1947	St. Joseph	. . . . .	16,170	454	2.80	3.30
1948	1936-1946	Boston City Hospital	McSweeney[13]	28,341	961	3.30	2.40
1948	1945	Detroit Hosps.	Mack[15]	37,028	1000	2.73	0.80
1948	1938-1947	Hague Maternity	Cosgrove[11]	67,959	2287	3.30	0.70
1948	1938-1947	Morrisania	Tamis[16]	8,356	127	1.50	3.30
1946	1930-1944	Chicago Lying-in Hosp.	Davis[12]	47,945	1824	3.90	0.60
1945	1934-1943	Boston Lying-in Hosp.	Irving[3]	45,218	1887	4.20	1.30
1944	1931-1941	Cleveland Maternity Hosp.	Barney[14]	23,396	1444	6.10	1.70
1944	1932-1942	Bronx Hosp.	Rosensohn[7]	20,763	494	2.40	3.20
1943	1932-1942	Philadelphia Lying-In	Mohler[6]	22,754	1322	5.80	1.96
1942	1937-1941	State of Massachusetts	DeNormandie[4]	333,731	11030	3.30	2.50
1938	1930-1937	Cedars of Lebanon	Lazard[5]	6,891	571	8.28	2.56
				674,722	23855	3.53	

TABLE XI. FETAL MORTALITY, 1928 TO 1937

STILLBIRTHS (11)		NEONATAL DEATHS (9)	
CAUSE	NO.	CAUSE	NO.
Abruptio placentae	3	Prematurity	3
Contraction ring	2	Atelectasis	2
Placenta previa	1	Congenital malformation	1
Toxemia with disproportion	1	Intracranial hemorrhage	1
Ruptured uterus	1	Undetermined	2
Prolapsed cord	1		
Undetermined	2		
Cesarean sections 188, fetal mortality 10.6%			

TABLE XII. FETAL MORTALITY, 1938 TO 1947

STILLBIRTHS (11)		NEONATAL DEATHS (8)	
CAUSE	NO.	CAUSE	NO.
Abruptio placentae	8	Prematurity	2
Ruptured uterus	2	Erythroblastosis	2
Placenta previa	1	Atelectasis	1
Undetermined	2	Congenital malformation	1
(Threatened uterine rupture)		Intracranial hemorrhage	1
		Undetermined	1
Cesarean sections 266, fetal mortality 7.8%			

These stillbirth and neonatal statistics include all babies of 1,000 grams and over. The total fetal mortality for the twenty-year period for the 454 cesarean sections was 9.0 per cent. In the first ten years for the 188 sections performed there was a gross fetal mortality of 10.6 per cent, while in the second decade this was reduced to 7.8 per cent for 266 cesarean sections, an improvement of almost 3 per cent. The gross fetal mortality following cesarean section is always higher than that following vaginal delivery because the indications for abdominal delivery are due to complications of pregnancy which by their very nature carry a high fetal mortality.

TABLE XIII. COMPARATIVE STATISTICS, FETAL MORTALITY

YEAR	AUTHOR	SOURCE	NO. OF SECTIONS	PER CENT	PER CENT MORTALITY
1949	. . . . .	St. Joseph Hosp., Chicago	454	2.8	9.0
1945	Irving[3]	Boston Lying-in	1887	4.2	6.8
1945	Free[18]	Chicago Lying-in	500	4.4	9.2
1943	Mohler[6]	Philadelphia Lying-In	1322	5.8	9.2
1942	Mathews[17]	Methodist Episcopal Hosp., Brooklyn	1116		6.0
1942	DeNormandie[4]	State of Massachusetts	11030	3.3	8.2
1940	King[8]	City of New Orleans	1108	2.0	10.8

Our average fetal mortality of 9.0 per cent for the twenty-year period and 7.80 per cent for the last decade compares favorably with those figures quoted by various authors in Table XIII. The 16,170 deliveries in the twenty-year period carried a fetal mortality of 3.28 per cent for there were 531 stillbirths and neonatal deaths during this period.

Summary

The tables and discussion have been presented to show the number, incidence, indications, mortality, and comparative statistics of 454 cesarean sections performed over a twenty-year period in a two hundred sixty bed general hospital.

This survey was divided into two ten-year periods to compare statistically the results of obstetrical supervision and to evaluate the effect of antibiotics, sulfonamides, and bank blood.

The incidence of cesarean section in the first ten-year period was 3.54 per cent and in the second period 2.44 per cent, a reduction of over 1 per cent.

The chief indications for cesarean section have remained about the same for both decades.

There has been a definite trend toward the low cervical cesarean section in the second ten-year period and, likewise, a decrease in maternal morbidity.

Cesarean hysterectomy was employed more frequently in the second decade and the incidence of 2.80 per cent compares favorably with the general average throughout the country. There was no maternal mortality in either decade following this procedure.

The cesarean section maternal mortality of 3.30 per cent is rather high for the 454 operations. For the first decade the incidence was 5.70 per cent which was reduced to 1.50 per cent for the second period; a reduction of 4.20 per cent. There were no maternal cesarean section deaths due to infection during the second ten-year period, probably due to the more frequent use of the Porro operation and the utilization of antibiotics, chemotherapy, and bank blood.

The infant mortality rate for the twenty years following cesarean section was 9.0 per cent, the incidence for the first period was 10.6 per cent, which was reduced to 7.8 per cent for the second ten-year period.

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References

1. Reis, R. A., and DeCosta, E. J.: J. A. M. A. **134**: 775, 1947.
2. Dieckmann, W. J., Bjork, F. J., and Aragon, G. T.: J. A. M. A. **137**: 1017, 1948.
3. Irving, F. C.: Am. J. Obst. & Gynec. **50**: 660, 1945.
4. DeNormandie, R. L.: New England J. Med. **227**: 533, 1942.
5. Lazard, E. M.: West. J. Surg. **46**: 6, 1938.
6. Mohler, R. W.: Am. J. Obst. & Gynec. **45**: 466, 1943.
7. Rosensohn, M., Kushner, J. I., and Wahrsinger, P. B.: Am. J. Obst. & Gynec. **48**: 274, 1944.
8. King, E. L.: Am. J. Obst. & Gynec. **40**: 860, 1940.
9. Studdiford, W. H.: Am. J. Obst. & Gynec. **45**: 103, 1946.
10. Douglas, R. G., and Landesman, R.: Am. J. Obst. & Gynec. **56**: 422, 1948.
11. Cosgrove, S. A.: Personal communication.
12. Davis, M. E., and Gready, T. G., Jr.: Am. J. Obst. & Gynec. **51**: 492, 1946.
13. McSweeney, D. J., and Hassett, A. J.: New England J. Med. **239**: 254, 1948.
14. Barney, W. R., Fish, J. S., and Riemenschneider, E. A.: Am. J. Obst. & Gynec. **48**: 733, 1944.
15. Mack, H. C., and Sidall, R. S.: Am. J. Obst. & Gynec. **56**: 60, 1948.
16. Tamis, A. B., and Clohr, J.: Am. J. Obst. & Gynec. **56**: 700, 1948.
17. Mathews, H. B.: in discussion of Manahan, C. P., Connally, H. F., Jr., and Eastman, N. J.: Am. J. Obst. & Gynec. **44**: 999, 1942.
18. Free, E. G.: Am. J. Obst. & Gynec. **49**: 401, 1945.

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Discussion

DR. AUGUSTA WEBSTER.—It is gratifying to note that in this hospital the current tendency to consider cesarean section the easiest way out of most obstetric difficulties has not prevailed. The percentage of sections has continued to decrease.

Mortality in cesarean section varies according to the indications for which the operation is undertaken. Each situation has to be evaluated according to its merits, and the obstetrician should be particularly careful in weighing indications. Every woman whose pregnancy is terminated by cesarean section is already in some sort of difficulty. The primary problem is to determine whether or not the best interests of the patient will

be served by a section. Whenever abdominal delivery is chosen the patient is at once placed in a much higher mortality group than when delivery is conducted by the vaginal route.

It is appreciated that the baby has certain inalienable rights and it is only in the most extreme situation that these conflict with the best interest of the mother. To jeopardize the mother for a baby who has manifested distress by irregular or failing heart tones is usually futile since such babies are more often than not already irreparably damaged. Nowhere in medicine is there more need for calm, considered medical judgment than when such a situation arises.

Repeat cesarean section accounts for approximately one-third of the operations just reported by Dr. Durburg. There is a growing tendency throughout the country to allow a selected group of patients who have had previous sections to deliver from below. This trend I believe to be unfortunate and hazardous. In a twenty-year period, from 1928 through 1947, there were forty-two ruptured uteri at the Cook County Hospital; nine of these followed cesarean section; seven occurred after classical sections and two occurred after low cervical sections. Six of these women were in varying degrees of labor and three ruptures occurred before the onset of labor. Six babies (66.6 per cent) were stillborn, and two mothers (22.2 per cent) perished.

No matter how carefully candidates with previous sections are screened for vaginal delivery, the behavior of the old scar is unpredictable. The fact that a woman has had intervening vaginal deliveries since her section does not guarantee her safety.

A Cook County Hospital patient, aged 21 years, had all the supposed safe criteria for vaginal delivery; she had delivered one 7 pound infant successfully from below; she then was subjected to a cesarean section for a nonobstetric condition. In her third pregnancy it was decided to allow her to attempt vaginal delivery. She progressed without incident to 7 cm. and plus 2 station when suddenly she grabbed her abdomen with both hands and cried out, "I'm tearing." Profound shock ensued, she was promptly operated upon, transfused twice, and although she recovered from the initial onslaught she died of peritonitis on her eleventh postoperative day. This accident occurred before the advent of the sulfonamides or penicillin and the fatality might now have been avoided. I cite her story only to illustrate that even in the most carefully selected patients, and under vigilant observation, an old scar may rupture without warning.

Another of the Cook County Hospital group was a woman aged 30 years, para iii, gravida iv, of 32 weeks' gestation, who had been delivered of her third baby by cesarean section because of placenta previa. She had had abdominal cramps and pain for seven hours at home which she considered to be indigestion and for which she took castor oil. Shortly after this self-medication she had a sudden sharp, tearing abdominal pain followed by profound shock. She was operated upon promptly after admission to the hospital, and blood and plasma transfusions were administered. The baby was stillborn, but the patient recovered after a stormy course and was discharged on the seventeenth postoperative day.

Hindman, in a recent paper encouraging pelvic delivery in selected cases for women previously sectioned for a temporary indication, states that approximately 4 per cent of previous sections can be expected to rupture from one cause or another. He further estimates that a 10 to 15 per cent maternal mortality and a 70 to 100 per cent fetal mortality may be expected where rupture of the uterus occurs.

If we accept these figures as average we must recognize the fact that the woman who is subjected to cesarean section not only has the hazard of the increased mortality of her first section, but by the very condition of subsequent pregnancies she places herself in an increasingly high mortality group. Instead of arguing the pros and cons of vaginal delivery following cesarean section, it would be more profitable for us, as the essayist has already pointed out, to consider very seriously the indications for every first cesarean section.

DR. M. EDWARD DAVIS.—I should like to present a few statistics from the Chicago Lying-in Hospital.

The data are divided into four periods of unequal lengths. In the first period—1931 to 1934—there were 500 cesarean sections and the incidence of the operation was 5.6 per cent; the second 500 operations were performed from 1934 to 1938 and the incidence was 5.5 per cent; the third 500 sections were done from 1938 to 1942 and the incidence was 4.4 per cent; 1181 cesarean sections were done from 1942 to 1948 and the incidence was 5.1 per cent. Thus, in a total of 2681 abdominal deliveries, the incidence was 5.1 per cent. It is noteworthy that the frequency of the operation has actually decreased over the years.

Maternal mortality has decreased appreciably in the four groups reviewed. In the first group, it was 1 per cent; in the second group, 0.6 per cent; in the third group, 0.4 per cent, and in the most recent group, 0.08 per cent. The loss of a single patient in the most recent group of 1181 operations emphasizes the safety of cesarean section in carefully selected individuals who are provided with all the safeguards of modern medicine. A fetal mortality rate of 5.9 per cent made up of a stillbirth rate of 1.2 per cent and a neonatal rate of 4.7 per cent in this same group of patients emphasizes the point that Dr. Webster made that abdominal delivery does not necessarily insure the birth of a living baby.

More than 90 per cent of the abdominal deliveries over the years were of the low or cervical type, laparotrachelotomy. The incidence of cesarean hysterectomy, however, has increased. The increased safety provided by hysterectomy in patients with complications has widened the use of this procedure.

There has been a radical change in anesthesia for cesarean section over the years. Local infiltration with Novocain was the anesthetic of choice until the last few years. The increased safety of spinal anesthesia in obstetrics and the many new refinements in its use have widened the application of this form of anesthesia. It is our impression that continuous spinal anesthesia, using Novocain, is the method of choice because of the increased safety of this procedure. Single injections of suitable drugs administered in minimal amounts with ample safeguards carry little risk today. It should be made clear, however, that it is far better to administer too little drug supplementing the spinal anesthesia by inhalation anesthesia at the end of an operation than to give too much drug to insure adequate anesthesia.

DR. GEIGER (Closing).—The only thing that I have to add is that we also have been using more spinal and less local anesthesia in our cesarean sections.

Fournier, J. C. Mussio, and de Santiago, A. Pou: Uterotubal Persufflation Curve in Myxedema. Effect of Thyroid Therapy, J. Clin. Endocrinol. 9: 285, 1949.

The effect of thyroid therapy on the uterotubal persufflation curve in seven patients with either hypothyroidism or myxedema is presented. In the normal woman, uterotubal persufflation results in a curve characterized by oscillations which are believed due to the muscular action of either the tubes or, possibly, the uterus. This study shows that, before treatment with thyroid, while there was patency of the tubes in all cases, there was almost complete lack of the characteristic oscillations and the gas passed at less than normal pressure. Following thyroid therapy, the pressure required for persufflation was elevated, and the normal or almost normal oscillations were present in all cases. The authors conclude that adequate thyroid therapy produces normalization of the uterotubal persufflation curve, as well as general clinical improvement and an increase of the basal metabolism to an approximately normal figure. HERBERT J. SIMON.

SARCOMA OF THE UTERUS*

W. C. DANFORTH, M.D., EVANSTON, ILL.

(From the Department of Gynecology and Obstetrics of Northwestern University Medical School, and of the Evanston Hospital)

AN ENORMOUS literature has accumulated concerning cancer of the uterus. In view of the tremendous importance of the subject this is quite as it should be. In comparison with the publications concerning cancer those which deal with sarcoma are very few. Many of these are mere case reports or brief communications dealing with two or three cases. In the past twenty-eight years in this country three noteworthy papers have appeared. Those of Evans[1] in 1928, Kimbrough[3] in 1934, and Novak[2] in 1937 present about all that is known. Clinically, the importance of cancer is greater than that of sarcoma because of its far greater frequency. For example, Evans, considering the material of the Mayo Clinic, found one sarcoma of the uterus to forty cancers. Kimbrough found one to thirty, Veit one to thirty-seven, and Frankel one to twenty-seven.

Standard textbooks of pathology as a rule give very little consideration to sarcoma of the uterus, and some gynecological texts deal with it rather briefly. It seems worth while to review the fourteen cases of sarcoma of the uterus which have occurred in our department of gynecology and obstetrics. The ages of these patients ranged from 35 to 69 years. In addition to these we have in our file slides of three uterine sarcomas, the source of which we do not know. We also have had the opportunity to see slides of a case in which carcinoma and sarcoma co-existed and another in which round-cell sarcoma of the cervix, or sarcoma botryoides, was found. In all, slides of nineteen cases were available for study.

Sarcomas may be divided according to the point of origin or according to the cell type. The point of origin may be in the musculature or connective tissue of the uterine wall, in the stroma of the endometrium, or in a previously existing myoma. Those which begin in the uterine wall or endometrium are referred to as primary while those which appear in a previously existing myoma are called secondary. Sarcoma of the cervix is very much less frequent than of the corpus. In the present series there were nine primary tumors and five which arose in myomas which were already present.

The expression "sarcomatous degeneration," which is sometimes used, should be discarded. A malignant tumor is very definitely a progressive growth.

If the tumors of the uterine corpus are classified according to cell type we find spindle-cell, round-cell, and mixed-cell varieties, while in the rare round-cell sarcoma which occurs in the cervix, more often in children, there may be an admixture of cellular elements which betoken an embryonic influence.

In this group there were no cases of stromal endometriosis, which in some cases exhibits a sarcomatoid character or which may end in true sarcoma.

In many tumors of spindle, round, or mixed cell types, giant cells may be found. Some writers, especially among the Germans, have employed the terms "sarcoma fusicellulare" or "globicellulare" and Albrecht[13] quoted Robert

*Presented before a regular meeting of the Chicago Gynecological Society, Dec. 17, 1948.

Meyer as characterizing one tumor as "globifusigigantocellulare partim atypicum." While these terms are descriptive, the Anglicized terminology seems adequate for routine use in this country. The presence of giant cells has, by some authors, been used as an evidence of a high degree of malignancy. This is not invariably true. When many giant cells, or abnormally large cells of varying size, many of which are multinucleated and closely crowded together, are found, the tumor must be regarded as highly malignant. The presence of one or more giant cells, surrounded by areas of little activity, with few mitoses, is rather an evidence of degeneration. The gigantism in such cases is the result of cytoplasmic confluence and does not denote an active growth. Areas of active and of less active growth may sometimes be found in the same tumor.

The tumors which arise from muscle tissue take their origin in poorly developed muscle cells. Whitridge Williams[7] in 1904 believed that he was able to demonstrate the change in a muscle cell which was becoming sarcomatous. The role of incompletely developed muscle cells in the development of sarcoma has received general acceptance. Because of the common mesodermic origin of the muscle, connective tissue, and vascular system of the uterus, sarcoma may arise from any of them.

It is sometimes difficult on microscopic examination to determine whether a tumor should be placed in the round- or spindle-cell group. In many cases the cells may be of both types, in fact a tumor exclusively composed of spindle cells is not often seen. The predominating variety may be ascertained by utilizing the simple device suggested by Robert Meyer who recommended examining the cells immediately beside the blood vessels. Cells of spindle type will be found parallel to the long diameter of the vessel while round cells will present the characteristic round outline. In other areas it may be difficult to determine of which type a certain area of cells is, as a bundle of spindle cells, if cut at right angles to the long diameter, may present a round outline which may deceive the examiner.

In the secondary tumors, or those which arise in previously existing myomas, spindle cells usually predominate. In only one of the secondary tumors in this group was the presence of sarcoma known prior to operation. This experience is in accord with that of the writers who have reported most of the series of cases in the literature. For example, in Novak's series, 36.4 per cent of the sarcomatous uteri were removed by subtotal hysterectomy. The diagnosis is, as a rule, made in the laboratory after operation. The history is not sufficiently distinctive to make an opinion of sarcoma very definite. The so-called rice-water discharge which is mentioned in the literature was seen in no case in this series. Bleeding, resembling that which is seen in carcinoma, is perhaps the most frequent symptom. A rate of growth which is more rapid than that usually seen in myomas is suggestive. In cases in which a number of tumors are present the sarcomatous change may be apparent in one and not in the others. If the tumor is contained within a myoma of some size, curettage may not be helpful, for the sarcomatous area may not be reached. The cut surface of the tumor, after removing the uterus, may be suggestive. The smooth homogenous character of the surface made by cutting contrasts with the familiar appearance of the surface made by sectioning a myoma. The comparison of the surface of a sarcoma which has been cut with raw pork, which was made by Kelly and Cullen[12] in 1909, has remained in the literature and has been repeated by almost every American writer. Albrecht[13] employed a comparison with cooked fish or lobster flesh.

The fact that in some reports the number of sarcomas as compared with other tumors is so much more than in others is probably the result of the trouble which some observers have had in distinguishing between a rather cellular myoma and a true sarcoma. There is no sharply defined dividing line between

myoma and sarcoma and some writers have evidently found it hard to separate the two, especially if the sarcoma is of a slowly growing type or the myoma is a particularly cellular one. The criteria given by Steiner[5] are useful. Sarcoma has less stroma, it is softer and more vascular, unencapsulated and cellular. The changes in the nuclei are suggestive, varying from very little change to extreme anaplasia. The nuclei are shorter, may stain more deeply and may be uneven in size and shape. There is an increased number of mitotic figures. Anaplasia may be present to a degree which renders impossible the determination of the tissue of origin, or a widely growing tumor, by extensive invasion, may cause it to be difficult to tell whether it began in the uterine wall or endometrial stroma.

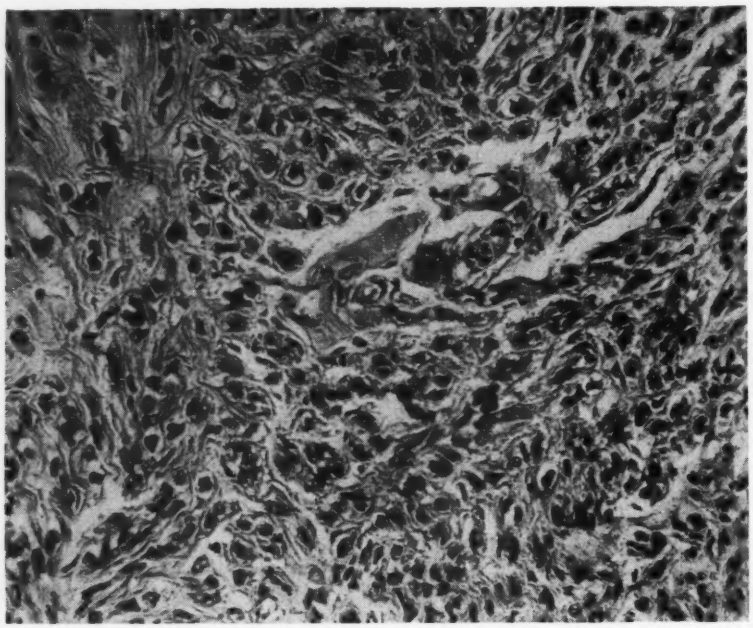

Fig. 1.—Spindle-cell sarcoma arising in a myoma. (×200.)

The degree of malignancy agrees rather definitely with the number of mitoses. Evans suggests an ingenious but rather complicated method of estimating the number of mitoses per cubic centimeter of tumor tissue and found that the clinical evidences of malignancy corresponded with the number of mitotic figures. Kimbrough made use of the same plan. Novak[2] suggests a simpler method which seems to serve the same purpose.

The sarcomas arising in myomas are almost always of the spindle-cell type and usually do not grow as fast as some of those which originate in the endometrium. In most of the reported series of cases there are instances in which subtotal hysterectomy was done and in which a cure was attained. Our experience was quite the same. One patient gave a history of having expelled a mass from the uterus, after severe bleeding, which was called a myoma upon examination by a laboratory in Florida. She came to us with a large pelvic mass which appeared to be a myoma. There had been further severe bleeding and she was quite anemic. A subtotal hysterectomy was done. There was a large mass which protruded into the uterine cavity and which was necrotic on its surface. Spindle-cell sarcoma was found on microscopic examination. The patient is alive and well eleven years after operation.

That subtotal hysterectomy cannot be depended upon to cure many patients is shown by the following experiences. One patient died within eighteen months with an obvious recurrence in the pelvis after subtotal hysterectomy. No autopsy could be obtained but a visit to the patient at home established the presence of a tumor. Another died some four or five years after operation. She was not then under our observation and such information as we could obtain indicated that the death was from malignant disease. Whether this was a recurrence of the original tumor or not could not be ascertained. A third patient, upon whom subtotal hysterectomy was done ten years ago, was operated upon a second time a few months later for a recurrence. A large pelvic tumor was found which

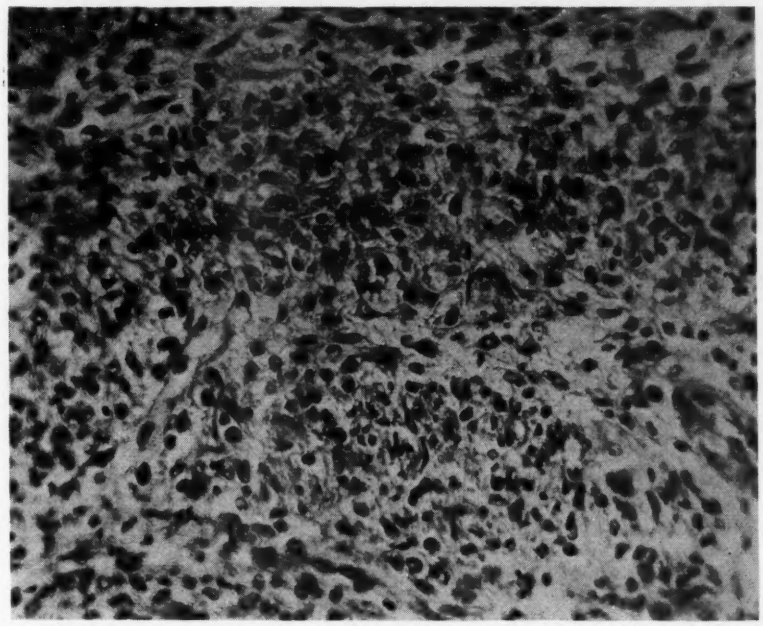

Fig. 2.—Spindle-cell sarcoma of uterine wall. Perforation of peritoneal surface and hemorrhage. (×200.)

could not be entirely removed. Death followed. This tumor was microscopically much more malignant than is the case in most secondary sarcomas. Although a fair number of cases are reported in which a subtotal operation was done and in which prolonged survival followed, the number of recurrences which we have seen would strongly indicate the advisability of total hysterectomy whenever the operator has the least reason for suspecting sarcoma. In addition, the precaution observed in many clinics, of opening the uterus in the operating room, especially when a subtotal operation is done, is important. This precaution may be extended to those cases in which myomas which seem at all soft are found. The finding of a suspicious area requires the removal of the cervix and adnexa. The frequent or almost routine use of the total operation, which is the practice in many active clinics today, here receives an added justification.

While sarcomas which arise in myomas in many cases are found at operation or autopsy to be confined within the tissue of the primary tumor, a sarcoma of the wall of the uterus, beginning intramurally, may push its way out into the uterine cavity. When this takes place, a part or all of the protruding portion may become necrotic. In one case of this series, already alluded to, this was seen. It may grow toward the serosal surface which it may penetrate. In one

of the cases of this series the tumor had come through the peritoneum and a sarcomatous mass 2 or 3 cm. wide was found on the surface of the uterus. In another case, when perforation of the peritoneum occurred, active intra-abdominal bleeding began, creating an emergency. The attending physician intervened at once, but, not suspecting sarcoma, a subtotal hysterectomy only was done. The patient recovered and a few weeks later the cervix and adnexa were excised. No further sarcoma was found microscopically in the tissue removed.

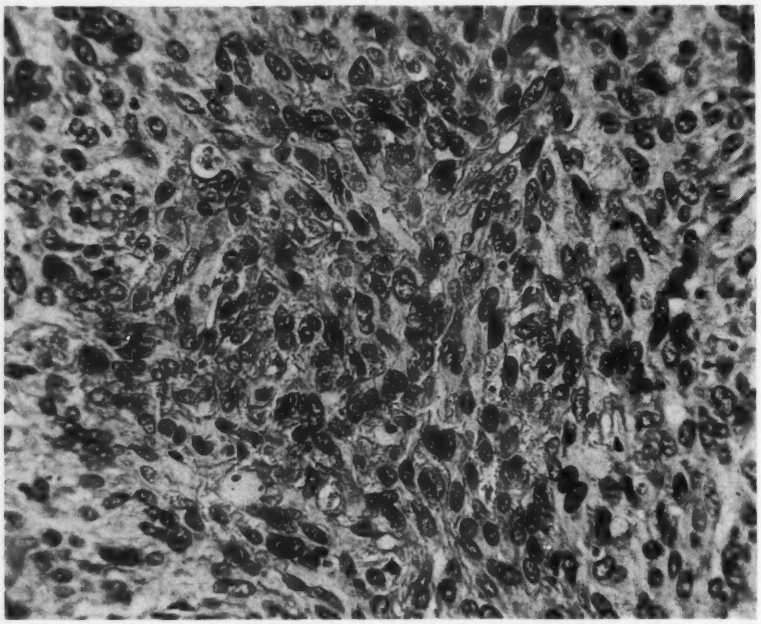

Fig. 3.—Sarcoma, probably of wall. (×160.)

In cases in which, after subtotal hysterectomy, unsuspected sarcoma is found, as a general rule deep x-ray therapy seems preferable to a second operative attack. It is interesting that no case has been reported in which sarcoma has appeared after treatment of a myoma by x-ray. As many thousands of such tumors must have been treated by radiotherapy it is scarcely possible that some sarcomas should not have been among them.

While the histologic morphology characteristic of sarcoma is usually present, Steiner[5] has reported a case in which, while the microscopic evidences of sarcoma were absent and few mitoses were seen, metastasis occurred and the tumor broke into blood vessels. This type of tumor is rarely seen but that such cases do occur is agreed to by Kaufmann,[17] Borst,[18] Aschoff,[15] Wolff,[14] and Ribbert.[16] However, most of the "recurring fibroids" reported by older authors were probably sarcomas, the true character of which had not been recognized.

Endometrial sarcoma arises from the endometrial stroma cells. The comparison which is sometimes made of the cells of some endometrial tumors with decidua cells seems quite justified as the decidua cells also arise from the stroma. These tumors may, at least at first, assume a polypoid character. In one of our cases such a polyp was removed by curettage, sarcoma being found on microscopic examination. Hysterectomy was done shortly afterward. Careful gross and microscopic examination disclosed no further evidence of sarcoma. The fact that no sarcoma was found after hysterectomy by no means indicates that, had curettage alone been done, a cure would have been attained. This is not an

uncommon experience with endometrial carcinoma. In this case the operator was fortunate in being able to attack the growth before it had time to invade but not necessarily before some sarcoma cells had found their way to other portions of the uterus.

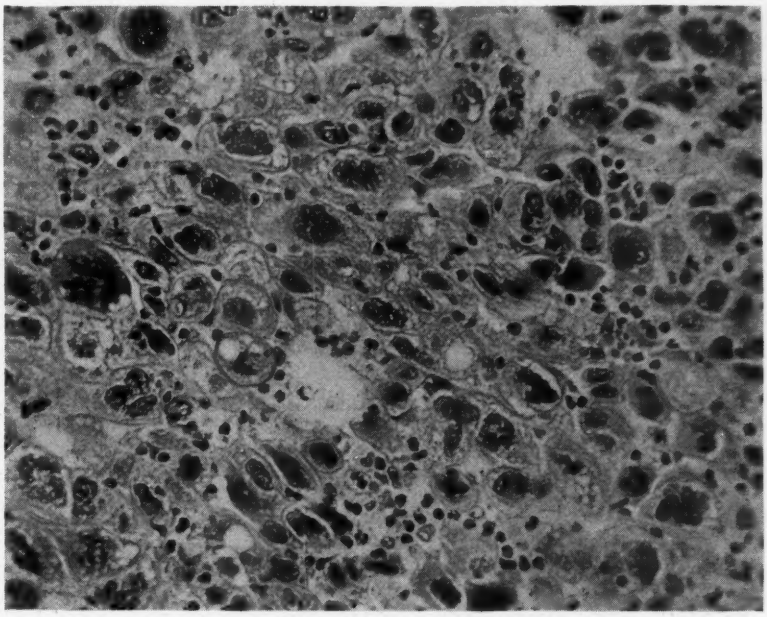

Fig. 4.—Endometrial sarcoma. Many very large cells of varying size, many multinucleated. A malignant picture. (×200.)

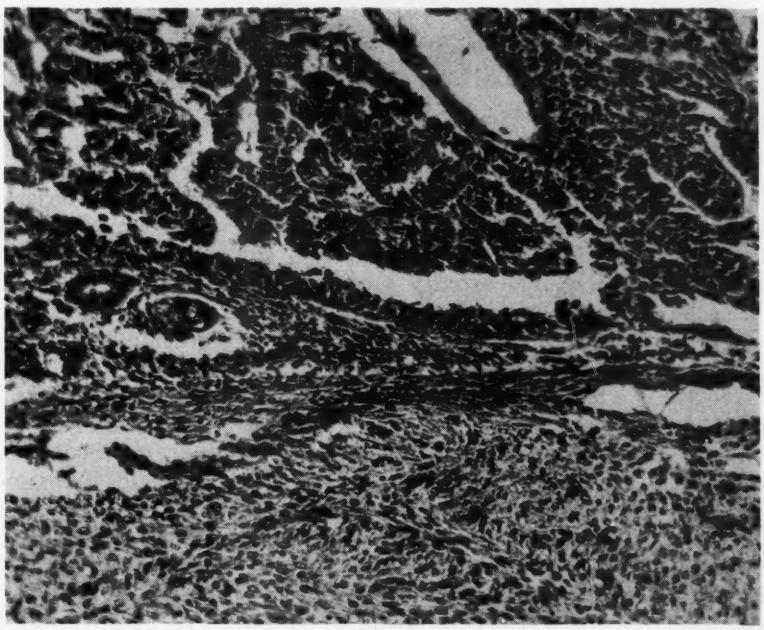

Fig. 5.—Spindle-cell sarcoma and adenocarcinoma in the same uterus. Case of Dr. J. F. Lutz, Lake Forest, Ill. (×80.)

Through the courtesy of Dr. J. F. Lutz of Lake Forest, Ill., I have had the privilege of seeing slides of a case in which carcinoma and sarcoma existed at the same time. Curettage done for diagnosis revealed the presence of sarcoma and, after hysterectomy, endometrial carcinoma was found in the uterine wall. A few areas of adenomyosis were also found in the myometrium. The sarcoma appeared to be primary in the wall of the uterus and the question as to whether it may have originated in one of the areas of adenomyosis was raised by one examiner. As the sarcoma had already invaded the wall rather extensively it was not easy to answer this question decisively but the character of the tumor would incline one to the belief that it arose in the uterine wall. In some areas the two growths were found side by side and in one place carcinoma was found within an area of sarcoma.

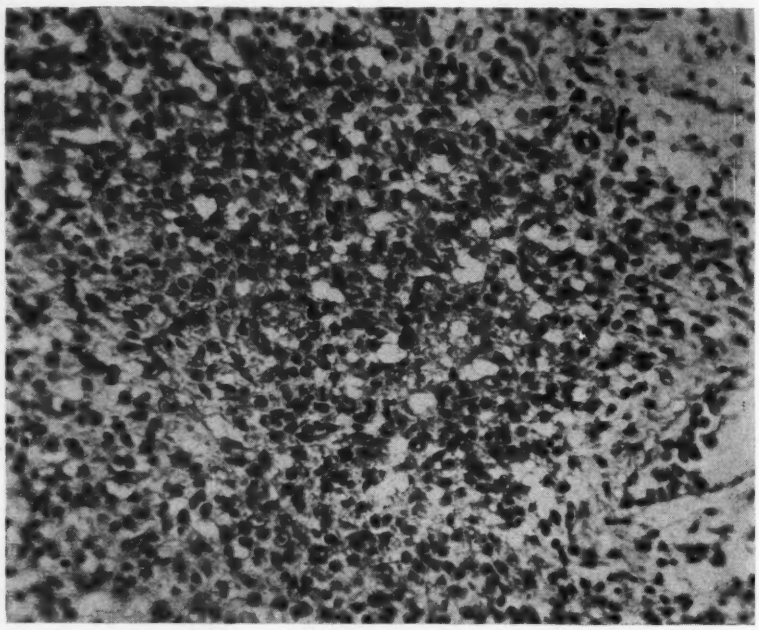

Fig. 6.—Round-cell sarcoma of cervix, sarcoma botryoides. Case of Dr. Floyd Sharp, Phoenix, Arizona. (×300.)

A number of cases in which carcinoma and sarcoma co-exist have been reported and some writers have used the term carcinosarcoma. The use of this term has been encouraged by the fact that in some cases the two tumors may be seen intermingled, which usually means the invasion of one tumor by the other. Cases have been reported in which a carcinomatous polyp is found and at its base or near it sarcoma may be seen. The suggestion has been made that in such cases the cancer may serve as an irritating factor encouraging the sarcomatous growth. There seems to be no convincing evidence of this. Tumor growth may occur in any tissue and it is perfectly possible for two tumors of varying character to be found in one organ, provided the tissues from which such tumors arise are found therein. When two tumors of invasive character are found close together it is entirely possible for one of them to invade the other which will give rise to a microscopic picture in which tumor elements of both types are found. The tumors, however, arise separately. When one is invaded by the other it is usually the sarcoma which is invaded by the carcinoma and metastases from such a combination of tumors are usually carcinomatous. There is no such hybrid tumor as carcinosarcoma and the term should be abandoned. This suggestion was also made in 1932 by Arthur Purdy Stout.[11]

Sarcoma of the cervix is far less frequent than of the corpus; Piquand,[19] in a series of 393 cases, found 325 in the corpus and 68 in the cervix. The grape-like sarcoma, or sarcoma botryoides, a round-cell sarcoma in which embryonic elements are sometimes found, is seen in infants and children and less often in adults. Most writers characterize it as uniformly fatal although Curtis[20] reports a case in which recovery occurred. We have had none of these in our own service but have had the opportunity of seeing slides of a tumor which was found in a young woman of 22 years. The patient died. The microscopic picture is that of a round-cell tumor with little stroma, indicating rapid growth. Beside the scanty stroma, mitotic figures are frequent and in a number of places tumor cells are seen within the lumina of small blood vessels. (These slides were seen through the courtesy of Dr. Floyd Sharp of Phoenix, Arizona.)

Summary

While sarcoma of the uterus is not a common tumor it is found with sufficient frequency that the possibility of encountering it should always be borne in mind. In the larger myomas, especially those with a history of rapid growth, it should be looked for. It may vary from a slowly growing tumor to extreme malignancy. Curettage, except in endometrial sarcoma, may not disclose its presence. Discriminating microscopic examination is needed to differentiate the less malignant sarcomas from cellular myomas. Treatment is primarily surgical and should include complete hysterectomy with excision of the adnexa. Postoperative irradiation should be used. As metastasis is more likely to occur by the blood stream than is the case in carcinoma, search should be made for secondary growths in distant areas, as the lungs. A case was recently reported by Kardash[21] in which metastases were found in the lungs and liver, and another by Gordon and Bohn[9] in which metastases were found in the lungs and brain.

References

1. Evans, N.: Surg., Gynec. & Obst. **30**: 225, 1920.
2. Novak, E., and Anderson, F. F.: Am. J. Obst. & Gynec. **34**: 740, 1937.
3. Kimbrough, R. A.: Am. J. Obst. & Gynec. **28**: 723, 1934.
4. Meyer, Robert: in Henke, F., and Lubarsch, O., editors, Handbuch der Speziellen Path., Anat., und Histol., Berlin, 1930, J. Springer, chap. xxiv.
5. Steiner, P.: Am. J. Path. **15**: 89, 1939.
6. Virchow, R.: Die Krankhafte Geschwülste **2**: 350, 1864-5.
7. Williams, J. W.: Am. J. Obst. **29**: 721, 1894.
8. Igna, E. J., and Mitchell, W. B.: Am. J. Obst. & Gynec. **45**: 303, 1943.
9. Gordon, W. H., and Bohn, S.: J. Michigan S. M. Soc. **38**: 398, 1939.
10. Visher, J. W.: Am. J. Surg. **31**: 181, 1936.
11. Stout, Arthur Purdy: Human Cancer, Philadelphia, 1932, Lea and Febiger.
12. Kelly, H. A., and Cullen, T. S.: Myomata of the Uterus, Philadelphia, 1909, W. B. Saunders Company.
13. Albrecht, H.: Biologie und Pathologie des Weibes, Halban und Seitz, Berlin, 1929, Urban und Schwartzenberg, vol. IV, p. 581.
14. Wolff, J.: Metastase gutartiger Geschwülste, Die Lehre von der Krebskrankheit, Jena, 1911, Gustav Fischer, vol. 2, pp. 403-406.
15. Aschoff, L.: Weibliches Geschlechtsapparat. Pathologische Anatomie, Ein Lehrbuch fur Studierende und Aertzte, ed. 7, Gustav Fischer, Jena, 1928, Chap. XI, p. 610.
16. Ribbert, M. W. H.: Geschwülstlehre fur Aertzte und Studierende, ed. 2, Bonn, 432, 1914, Friedrich Cohn, p. 432.
17. Kaufmann, E.: Pathology for Students and Practitioners. Trans. by Reimann, Philadelphia, 1929, P. Blakiston's Son & Company, vol. 3, p. 1666.
18. Borst, M.: Echts Geschwülste (Gewächse, Blastome) Path. Anat. Ein Lehrbuch fur Studierende und Aertzte, Aschoff, L., Jena, 1928, Gustav Fischer, ed. 7, vol. 1, p. 738.

19. Piquand: Les Degenerescenses malignes de Fibromyomes de l'Uterus, These de Paris, 1905, Rev. de gynéc. et de chir. abd. **9**: 1905.
20. Curtis, A. H.: Textbook of Gynecology, ed. 5, Philadelphia, 1946, W. B. Saunders Company, p. 347.
21. Kardash, Theodore: Am. J. Obst. & Gynec. **56**: 566, 1948.

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Discussion

DR. HERBERT E. SCHMITZ.—It is interesting to read Dr. Danforth's presentation of uterine sarcoma with his classification based on the undifferentiated mesenchymal cell: namely, round-cell, spindle-cell or mixed-cell varieties. Although this classification is widely accepted by clinicians, the pathologists have abandoned it for one which gives us the origin of the sarcoma whenever possible; namely, leiomyosarcoma, fibrosarcoma, endometrial sarcoma, and using the classification of undifferentiated sarcoma for those tumors where the tissue of origin is not clear. If we accept this latter classification we may then proceed to establish their resistance or sensitivity according to the degree of differentiation and undifferentiation.

The unripe blastomas are composed of either small round cells or small spindle cells of low differentiation or high degree of anaplasia. They are clinically very malignant, form metastases early and freely, and are highly radiation sensitive. The cells of middle ripe sarcoma have attained a certain degree of differentiation. They form fibrosarcomas and myxosarcomas. The sarcomas occurring in myomas belong in this group which comprises the largest group of connective tissue tumors of the uterus. They are clinically less malignant and form metastases rarely. Novak believes that this fact is responsible for the rare occurrence of sarcoma in previously irradiated myomatous uteri. He suggests that the sarcoma is destroyed in most instances. The ripe connective tissue tumors are the myofibromas. They are mostly composed of relatively fully differentiated, spindle-shaped smooth-muscle cells and ripe connective tissue fibers. They are clinically benign.

The status of the carcinosarcoma is a questionable one. It is thought not to be collision of two separate tumors but rather a tumor in which spindle-shaped elements are intimately intermingled with more or less typical epithelial cells. It is exceedingly difficult in many instances to state whether both stroma and epithelium have assumed malignant properties or whether the epithelial cells have merely become spindle shaped.

As Dr. Danforth points out, "the grapelike sarcoma, or sarcoma botryoides, [is] a round-cell sarcoma in which embryonic elements are sometimes found." Novak says that "among the sarcomatous elements one may find also other mesodermal elements, especially embryonic striped muscle, with less frequently cartilage." It seems, therefore, that in these tumors the round cells are undifferentiated elements; hence, to call these mixed tumors of the cervix would be more exact and descriptive. Meikle brings to our attention the fact that mixed tumors occur in the vagina, cervix, and body of the uterus, and they are found in this order according to age; the vaginal type being found in the very young.

I must support wholeheartedly the essayist in his plea for total hysterectomy in preference to the subtotal operation. The unrecognized sarcoma is but another reason to add to the many already established to demonstrate the advantages of the total procedure.

DR. FREDERICK H. FALLS.—I agree with the essayist on practically all the points that he makes in the paper, but would like to emphasize a thing that he spoke about but did not emphasize, the relationship between fibroids and malignant tumors of the uterus. Our textbooks say that fibroids of the uterus are benign tumors and if removed will not recur. Therefore, aside from the hemorrhages they produce and the degenerative changes that may occur in the way of associated inflammatory reactions, they are innocuous. But as we review these slides, we see that time after time when these malignant changes occur, there was a fibroid preceding, so we cannot say that a fibroid of the uterus is a

benign tumor. Fibroid areas can become malignant either in a sarcomatous sense or associated with epitheliomatous change, that is carcinomatous. The reason for this lack of understanding of this condition I believe to be a psychological one.

If a patient enters the Cook County Hospital and comes to the ward as having a fibroid of the uterus, we decide that because she is bleeding and has a fibroid, operation is indicated. We remove the uterus and send it to the pathologist and the report comes back, "fibroid of the uterus plus a carcinoma or sarcoma of the body of the uterus or cervix." That case goes down in the statistics not as a fibroid but as either a carcinoma or sarcoma. For that reason the importance of looking for malignancy in connection with fibroids of the uterus has been neglected. At the University of Iowa I became interested in this subject and analyzed the cases that we had in the five years I was there. In addition to the degenerative changes that occur in fibroids for which we operated, we found on examination carcinoma of the cervix associated with fibroids. We also found the case records of a number of patients who came in with carcinoma of the stomach in which on further inquiry it was learned that the patients had previously been operated upon for fibroid of the uterus. Taking all the cases of fibroids seen at the clinic, the incidence of fibroids that had malignant degeneration was 13.5 per cent. I think that is a rather important thing for us to keep in mind.

Looking beyond that, what does this mean? We think it means that in any case in which there is a diversion from the normal which forms a condition that we call tumor, be it fibroid, carcinoma, or sarcoma, the same factors are at work and the presence of fibroid is simply one step closer to the condition we call sarcoma, and that in that same uterus because of this biological abnormality we call fibroid we are closer to a biological change which we call carcinoma. That is why we should look particularly for malignant tumors in uteri which have these benign tumors.

A procedure was hinted at by Dr. Danforth which I think might be carried a little further, namely, opening the fibroid uterus at operation and looking for these changes that are characteristic of sarcoma. We think one might very well add to that a frozen section of a portion of the tumor, if the cursory one is at all suspicious that these changes may be sarcomatous. It is not easy to differentiate between a rapidly growing fibroid and a slow-growing sarcoma. Along that line the statement of Fränkel is interesting. He went over a large number of slides collected over many years in Vienna and found 2 per cent sarcomas. Later on in his career he examined that same group of slides; with the additional experience he classified 10 per cent as sarcoma, which shows that the examiner and his experience have a good deal to do with how these tumors are classified, whether borderline on malignancy or straight benign tumors.

DR. GEORGE H. GARDNER.—The usual custom in clinical teaching of referring to sarcoma as one of the degenerative phenomena in myomas is obviously a misusage of terms; certainly it is a proliferative process. Next he emphasizes the absolute necessity of opening surgical specimens immediately in the operating room; in this way unsuspected pathology is recognized promptly and treatment made compatible with whatever is encountered. Furthermore, we must all recognize that innumerable problems arise in defining the exact histologic criteria for the diagnosis of sarcoma. The incidence of sarcoma reported from various clinics varies markedly depending on their individual criteria for this diagnosis. Obviously sarcoma of the uterus is a rare tumor, otherwise Dr. Danforth would have had many more cases to report from the vast experience of the Evanston Hospital. It is also probable that only a modest percentage of his fourteen arose in myomas.

So far as treatment is concerned, experience does not seem to confirm the impression that postoperative radiation is beneficial. I am impressed that when dealing with uterine sarcoma we have really given the patient our all at the time of the original surgery. In this regard it may be pertinent that Dr. Schmitz, who is not at all allergic to radiation therapy, did not mention it as part of the indicated follow-up treatment in these patients.

DR. DANFORTH (Closing).—I want to thank Dr. Schmitz for giving us the classification which he did and which I think in many ways is better than the one I used.

Dr. Falls spoke of the co-existence of cancer and myoma. As myoma is an extremely common tumor and carcinoma is not particularly uncommon, it seems to me these two can co-exist without a causative relationship. I think it has already appeared in the literature and if I had a case of sarcoma of the endometrium associated with myomas I would be rather skeptical whether the myoma had anything to do with the endometrial sarcoma. I would be very happy indeed if I could be confident that a frozen section made in the operating room would settle the diagnosis. I have had a fair amount of experience with frozen sections and many of them are not too satisfactory. Unless one has someone at hand who is expert in making frozen sections, I do not think that this is a satisfactory method. After working with this series of slides as long as I have, I find it occasionally difficult to tell whether the tissue is a cellular myoma or a sarcoma. I would not be too confident of a quick diagnosis made by a frozen section.

I want to thank Dr. Gardner for backing me up on the condemnation of the term degeneration.

Lloyd, C. W., Hughes, E. C., Eva, M. L., and Lobotsky, J.: The Urinary Excretion of Chorionic Gonadotropin by Human Females Following Parenteral Administration of Aqueous or Beeswax Solutions, J. Clin. Endocrinol. 9: 268, 1949.

The authors present a study of the urinary excretion rate of chorionic gonadotropin in beeswax or aqueous solution. They injected ten women with 5,000 I. U. of the hormone in aqueous or beeswax solution. Eight of these patients had normal cyclical menstruation and two were menopausal. When the chorionic gonadotropin was given in aqueous solution, excretion began sooner than when given in beeswax. However, as might be anticipated, the chorionic gonadotropin was recoverable from the urine for a longer time when given in beeswax solution. This solution caused considerable local reaction and, in one patient, fever of two days' duration occurred.

Inasmuch as a low excretion rate of chorionic gonadotropin is found in many women who subsequently abort, a rational method of treatment of threatened abortion should be the administration of large amounts of this hormone. This increase in the amount of circulating chorionic gonadotropin should stimulate the corpus luteum to further activity. The authors were able to raise the titer of urinary gonadotropin in six women who were threatening to abort by administering the hormone in doses of 5,000 to 10,000 I. U. daily. The low excretion rate was raised to a normal range while the material was being given, but returned to a low range when administration was stopped. No definite conclusions as to the efficacy of this method of treatment of threatened abortion were drawn.

HERBERT J. SIMON.

Von Tachezy, Rudolf. Sex Hormone Implantation in Hypogonadism, Gynaecologia 125: 193, 1948.

From the Obstetrical and Gynecological Department in Prague Dr. Tachezy reports twenty-five cases of female hypogonadism treated by implantation of oestradiol and progesterone. The dose implanted was 100 mg. of each substance.

The most striking results were obtained in the appearance of secondary sex characteristics. There are excellent "before and after" photographs showing breast and genital development. These changes occur on the average about eight months after implantation. In those cases where primary amenorrhea existed the results were not consistent. The hormones were inserted in the abdominal muscles.

EUGENE N. SCADRON.

A STUDY OF NEONATAL DEATHS*

A Six-Year Review

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DURING the past twenty-five years, the active participation of obstetricians and gynecologists in the various maternal welfare programs is showing results in the steady decrease in maternal and neonatal deaths. However, the decline of the neonatal rate has been of a lesser degree than of the maternal death rate. This is due in part to the greater number of uncontrollable factors resulting in neonatal death. In this study we are attempting to show some of the reasons for these deaths and to present material which may serve as a basis for further investigation. We accept death in those infants grossly malformed, for such deaths cannot be prevented by any means available at the present time. Some of the remaining deaths might have been avoided by the general application of the knowledge we now possess, and it is this group which may in part yield to attack and lower the neonatal death rate further.

A child is considered liveborn in the United States if there is any sign of life (heartbeat, muscular movement, or respiration) after it is delivered altogether (head, trunk, and limbs) outside of the body of the mother, whether or not the cord is cut. The neonatal period is considered to be that time from birth to the end of the first month of life.

Material

In the six-year period from Jan. 1, 1942, to Dec. 31, 1947, 14,872 infants were born at St. Anne's Hospital. Of this number, 258 were stillborn, or 17.6 per thousand live births. Two hundred forty-three or 16.6 per thousand were born alive and died within one month. Necropsy examinations were performed on 237, or 97.5 per cent, of the neonatal infants.†

Management

All patients were under the care of their private physicians, the majority of whom were general practitioners. Consultation by certified specialists was available at all times, and the Chicago Board of Health rules and regulations were rigidly enforced by the hospital authorities. Vitamin K was administered to all patients on admission as a routine procedure. Oxytocics were not permitted prior to the third stage of labor, and for this reason they are not mentioned as an etiological factor in neonatal deaths. An active blood bank in the hospital makes blood of proper type and Rh group available at all times. A modern fully equipped nursery for premature infants is maintained separately from the two nurseries for newborns and is under the direct supervision of a certified pediatrician. Constant observation and care are given by an adequate number of registered nurses trained in the care of premature infants.

*Presented before the Chicago Gynecological Society, Dec. 17, 1948.

†One hydrocephalic infant lived beyond the neonatal period, but was included in this study.

In this study 231 women delivered 243 infants that died within the neonatal period. There has been no attempt to give corrected mortality statistics; thus, all infants with congenital defects and previable prematures are included. The anatomic diagnosis as to the cause of death was not altered, and each record is presented without personal interpretation. In Table I are shown the obstetrical statistics from 1942 to 1947. Live births totaled 14,614; the stillbirth rate determined was 17.6 per thousand live births; the neonatal death rate, 16.6 per thousand live births; the maternal death rate, 0.89 per thousand live births. To obtain an accurate picture of the mortality in childbearing in this hospital, stillbirths and neonatal deaths are shown in this table.

Age Distribution

The greatest number of infant deaths occurred in the maternal age group 21 to 35 years. Among the 231 women in this series, 186 were in this group. Age was not a significant factor in the percentage of infant mortality.

TABLE I. OBSTETRICAL STATISTICS

	1942	1943	1944	1945	1946	1947	TOTAL	RATE*
Live births	2405	2154	1966	1976	2849	3264	14,614	
Stillbirths	43	35	30	36	53	61	258	17.6
Neonatal deaths	33	38	37	26	50	59	243	16.6
Maternal deaths	2	4	2	3	1	1	13	0.89

*Per 1,000 live births.

Distribution by Parity

An infant was considered viable if he reached the twenty-eighth week of gestation. A woman having borne a child to or beyond the period of viability for the first time was considered a primipara. A gravida i, who delivered a live infant of less than twenty-eight weeks' gestation, was considered a nullipara. Of all the women, 42.5 per cent were primiparas. The parity and frequency of pregnancies in this group were studied, with the thought that frequent pregnancies or the function of old parous uteri might contribute an etiological factor in these deaths. This was not borne out in this study, the majority of deaths occurring in primiparous patients.

Prematurity has been found to be the most important single etiological factor in all studies of neonatal deaths. If there is to be any marked salvage in these fetal deaths, the greatest opportunity for improvement lies in the group of premature infants. For that reason prematurity will of necessity be stressed more than the term group. Only 35 per cent of infants reached term, and congenital defects accounted for the deaths of many of these. The prevention of premature labor and the prevention or control of complications requiring induction of premature labor will without question halve the mortality. Hess[3] in his book on premature infants gives syphilis as a major cause of spontaneous premature labor. In this series there was not a single Kahn or Wassermann positive patient, and all patients had these laboratory procedures done. Eastman[2] shows convincing evidence that economic status, dietary deficiency, and race influence premature labor. These items played no essential part in this study.

Onset of Labor

The onset of labor was spontaneous in 203, or 87.9 per cent, of these cases. Cesarean section was considered an induced labor when used to terminate labor before the onset of pains, and accounted for 20 of 28 induced labors. The incidence of induced labor was 12.1 per cent.

Period of Development of the Fetus

The University of Chicago has used over a long period of time a standard for determining the period of development of the fetus. Three factors are used in this standard: (1) the period of gestation in weeks based on menstrual history and physical findings; (2) the weight of the child; (3) the crown-rump length of the fetus. In the records studied the crown-rump length of the fetus was not listed frequently enough to be used. With this item lacking it was decided to use the length of gestation and the weight of the infant separately, and then compare the two. This revealed that 37.4 per cent of all infants did not reach the 28 weeks of pregnancy, and statistically are classified as previable. Only 35 per cent of these infants reached term. It is readily apparent that the greatest opportunity for salvage lies in this group which did not reach term, and where prematurity was at least a contributing factor in the death of the infant. Table III, a study of infant weight, reveals that 26 per cent are in the previable group, and 68 per cent weighed less than 2,500 grams. The comparison of the length of gestation and weight of the infants is interesting in that the weights in the previable group were greater than the length of pregnancy indicated, but at term the infants did not reach mature weight expected of that period of pregnancy. This relative immaturity in the term group serves as a possible factor. Congenital defects, which in the majority of instances occurred in infants delivered at term, also added to substandard weights of this group.

TABLE II. PERIOD OF GESTATION (BASED ON CHICAGO LYING-IN STANDARD)

	1942	1943	1944	1945	1946	1947	TOTAL	PER CENT
Abortion Less than 22 weeks	0	0	3	1	0	6	10	4.2
Previable 22 to 28 weeks	10	16	10	10	20	15	81	33.2
Viable 29 through 38 weeks	14	10	7	4	12	21	68	27.9
Term 39 through 42 weeks	8	12	17	11	18	17	83	34.2
Postmature Over 42 weeks	1	0	0	0	0	0	1	.5
Total	33	38	37	26	50	59	243	100.0

TABLE III. INFANT WEIGHTS

	1942	1943	1944	1945	1946	1947	TOTAL	PER CENT
Abortion Less than 400 grams	0	2	2	0	1	2	7	2.9
Previable 400 to 999 grams	7	11	8	4	9	17	56	23.0
Viable 1,000 to 2,499 grams	16	12	15	12	24	25	104	42.5
Term 2,500 to 4,500 grams	9	13	13	10	15	15	74	30.7
Postmature Over 4,500 grams	1	0	0	0	1	0	2	0.9

Method of Delivery

The method of delivery of the premature infant has been a debatable subject over a period of time. Plass[6] showed that operative interference in breech presentation increased fetal mortality as high as 400 per cent. McCormick[5] in his aphorisms states the more premature the infant the larger the episiotomy.

There is that group who believe that all premature infants should be delivered by prophylactic forceps, and there is another group who feel that fundal pressure, as an aid to spontaneous delivery with episiotomy, is to be preferred to forceps. Others believe that cesarean section is the answer to lowered infant mortality, especially if the pregnancy is complicated and must be terminated. The opinion in regard to the proper method of delivery of the premature infant is varied, and of necessity each case should be individualized. In any consideration of the method of delivery of a premature infant, it might not be amiss to reflect upon the care given a premature infant once it reaches the nursery for premature infants. These infants, in addition to receiving oxygen and heat, are subjected to a minimal amount of handling, frequently not being weighed until they are better established in life. This picture may be far different from the one presented in the delivery room just a few minutes before. It might be well to examine our neonatal deaths with this in mind, to determine whether or not a more conservative type of delivery might not decrease some of these mortalities in the premature. In our series (Table IV) 129 (53.3 per cent) were spontaneous deliveries.

Breech deliveries accounted for 44 deaths (18 per cent). The high incidence of breech delivery deaths can be accounted for in part by the increased incidence of breech presentation in premature labor, the normal increased mortality in breech presentation, and the increased tendency on the part of physicians to interfere in breech presentations. No attempt has been made in this study to distinguish between spontaneous breech delivery, spontaneous delivery with manual or instrumental aid to the aftercoming head, and breech extraction, because in this institution all records did not adhere to the above classifications, and an honest evaluation could not be presented. Forceps procedures were performed 39 times (16 per cent). In four of the midforceps procedures, Dührssen's incisions were used. Cesarean section accounted for 22 (9 per cent) of the fetal deaths. These deaths were due in most part to the complication of pregnancy which indicated the section. Version and extraction accounted for nine deaths; the greatest number of these, six, occurred in the delivery of the second twin. The outstanding mortality is in breech delivery. Some salvage should be made by closer regulation and study of breech deliveries. The more rigid application of conservative management in breech deliveries should lower the present 18 per cent mortality.

TABLE IV. METHOD OF DELIVERY

	1942	1943	1944	1945	1946	1947	TOTAL	PER CENT
Spontaneous cephalic deliveries	25	19	13	17	25	30	129	53.3
Breech deliveries	5	6	8	4	8	13	44	18.0
Prophylactic forceps	0	4	5	3	7	8	27	11.0
Low forceps	0	2	1	0	1	0	4	1.7
Midforceps	1	2	0	2	2	1	8	3.3
Cesarean section	2	4	7	0	6	3	22	9.0
Version and extraction	0	1	3	0	1	4	9	3.7
Total	33	38	37	26	50	59	243	100.0
Dührssen's incisions	0	1	0	1	1	1	4	1.7
Bag inductions	0	0	0	0	0	3	3	1.2

Complications of Pregnancy

Many of the neonatal deaths are directly or indirectly related to the maternal complication which may have caused the pregnancy to be terminated prior to term (Table V). Many of these cases had more than a single complication.

Premature labor was the most frequent complication found occurring in 144, or 64.8 per cent, of these cases. (When one considers that the majority of infants with congenital defects reached term, and accounted for 20 per cent of the total deaths, we can readily see that premature labor was a most formidable complication.) Toxemias of pregnancy occurred twenty-eight times (12.6 per cent). This group presents a point which might have a direct bearing on lowering some of the fetal mortality. Eighty per cent were hospitalized only after the toxemia was severe. Some patients had presented toxic manifestations for a period of six weeks prior to hospitalization. This group of patients with toxic manifestations over a period of time without early hospitalization and active treatment did not receive adequate prenatal care, and under ideal treatment some of these infants should have been saved. Stander[4] reports a fetal mortality of 12.2 per cent in severe pre-eclamptics, and Potter,[7] reports eighteen per cent fetal mortality in the late toxemias of pregnancy. While our figures compare favorably with those of both of these investigators, we are not satisfied with our mortality figure. Placenta previa occurred fourteen times, and some of these deaths might have been avoided if the application of knowledge we now possess could have been applied to these patients. In this group of patients the uterus was emptied as soon as a diagnosis of placenta previa was made. In ten instances cesarean section was chosen as the means of evacuating the uterus, and delivery through the birth canal accounted for the remainder. This form of treatment of necessity increased fetal mortality. With the availability of blood in this institution, the pursuing of an intelligent conservative course in these cases might have carried some of these infants closer to term, and thus have lowered this mortality. The pendulum is swinging more and more in this direction, and good results are being reported both in this country and in England. These cases must be selected carefully so that maternal mortality is not increased in our endeavor to lower the fetal mortality of placenta previa. Premature separation of the placenta occurred in five cases (2.25 per cent), and prolonged labor in twenty-one cases (9.45 per cent). Extrauterine pregnancy (abdominal) accounted for one fetal death.

TABLE V. COMPLICATIONS OF PREGNANCY AND LABOR

	1942	1943	1944	1945	1946	1947	TOTAL	PER CENT
Premature labor	21	22	18	15	29	39	144	64.80
Toxemia	2	6	4	4	6	6	28	12.6
Prolonged labors	4	3	3	2	4	5	21	9.45
Placenta previa	2	2	4	0	3	3	14	6.3
Premature separation of placenta	0	1	1	1	0	2	5	2.25
Prolapsed cord	0	0	0	1	1	0	2	0.90
Extrauterine pregnancy	0	0	0	0	1	0	1	0.45
Hydrocephalus	2	2	0	0	1	2	7	3.15
Breech presentations	5	6	8	4	8	13	44	19.00
Transverse presentation	0	1	1	0	1	1	4	1.8
Twin pregnancies	0	3	3	0	6	7	19	8.65
Triplet pregnancy	0	0	0	0	0	1	1	0.45
Retained placenta	0	0	0	0	1	0	1	0.45
Total	36	45	42	27	61	79	290	

Stages of Labor (Tables VI and VII)

The length of the first stage of labor can be influenced by the condition of the cervix, the parity of the mother, the strength and frequency of uterine contractions, and the size of the infant. The pregnant uterus, prior to term, frequently exhibits a long and uneffaced cervix, and is not considered "ripe" for

induction. Experience has shown that such cases are not easily induced. Ninety-seven per cent of all cases delivered through the birth canal had a spontaneous onset of labor, many demonstrating an "unripe" cervix on admission. Theoretically, the unprepared cervix should increase the length of labor. This is in a degree compensated for by the smaller infant requiring less cervical dilatation to effect passage. In an attempt to study these points the first stage of labor (Table VI) was divided into patients delivered through the birth canal prior to the twenty-eighth week of gestation and those delivered at or after the twenty-eighth week. Further subdivision of these groups into nullipara, primipara, and multipara gives an analysis of the first stage from the size of the infant, the parity of the patient, and the length of gestation. Sixty-two and one-half per cent of all patients had a first stage of labor less than twelve hours. Prolonged labor (twenty-four hours or more) was chiefly confined to primiparous pregnancies of twenty-eight weeks or more. This table seems to indicate that the unprepared cervix did not produce any appreciable prolongation of the first stage of labor. In the previable group (Table III), 62 of the 75 patients had a second stage of labor of less than one hour and only four patients over two hours. In the viable and term group, 108 of the 145 patients had second stages of less than one hour, and fifteen (10.4 per cent) over two hours. Approximately three-fourths of the total number had second stages less than one hour.

TABLE VI. STAGES OF LABOR: FIRST STAGE

	UNDER 28 WEEKS					OVER 28 WEEKS			
	PARA 0	PRIMIP-ARAS	MUL-TIP-AROUS	TOTAL	PER CENT	PRIMIP-ARAS	MUL-TIP-ARAS	TOTAL	PER CENT
1 through 6 hours	10	8	16	34	15.5	13	39	52	23.4
7 through 12 hours	5	10	4	19	8.5	18	15	33	15.1
13 through 18 hours	4	4	4	12	5.4	13	11	24	10.5
19 through 24 hours	5	2	1	8	4.0	7	10	17	7.5
25 through 30 hours	1	0	0	1	0.4	4	0	4	1.8
Over 30 hours	0	0	1	1	0.9	12	3	15	6.5
Total	25	24	26	75	34.7	67	78	145	64.8
Unrecorded	0	0	0	0		0	1	1	0.5
Total	25	24	26	75		67	79	146	

Under 28 weeks	75
Over 28 weeks	145
Unrecorded	1
Total	221

TABLE VII. STAGES OF LABOR: SECOND STAGE

	UNDER 28 WEEKS					OVER 28 WEEKS			
	PARA 0	PRIMIP-ARAS	MUL-TIP-ARAS	TOTAL	PER CENT	PRIMIP-ARAS	MUL-TIP-ARAS	TOTAL	PER CENT
Under 30 min.	16	8	17	41	18.5	16	39	55	24.9
30 min. to 1 hour	3	12	6	21	9.5	26	27	53	24.0
1 to 2 hours	5	2	2	9	4.0	14	8	22	9.9
2 to 3 hours	1	1	1	3	1.5	7	2	9	4.0
3 to 4 hours	0	1	0	1	.5	4	2	6	2.7
Total	25	24	26	75	34.0	67	78	145	65.5
Unrecorded	0	0	0	0		0	1	1	0.5
Total	25	24	26	75		67	79	146	

Length of Life

The inability of a certain number of premature infants, regardless of weight or period of gestation, to tolerate extrauterine existence accounts for an undeterminable percentage of these deaths, but the method of delivery, the complications of labor and the immediate care given the premature infant after delivery are factors influencing the length of life of the infant. Twenty-seven and one-fourth per cent of all infants died within the first four hours of life, and 56.5 per cent of all infants died within the first twenty-four hours. Of those under twenty-eight weeks of pregnancy, 55 (70 per cent) died within the first twenty-four hours, and only one child survived beyond the seventh day. In the group over twenty-eight weeks, 83 (49.9 per cent) infants died within the first twenty-four hours. The life expectancy of a viable premature infant increases tremendously if it survives the first twenty-four hours of life. This finding remains fairly constant in all reports.

Anatomic Causes of Death

The anatomic causes of death have been listed alphabetically. Prematurity was an etiological factor in the death of 52.9 per cent of these infants. This compares favorably with the fact that 68 per cent of these infants weighed less than 2,500 grams. Intracranial hemorrhage in this series accounted for thirty deaths, 12.5 per cent (Table VIII). The majority of these infants were term babies and had been subjected to operative deliveries. McCormick[5] in 1938 found that intracranial hemorrhage accounted for over 50 per cent of the premature deaths, and Bundesen and co-workers[1] found intracranial hemorrhage to occur in 22 per cent of their total deaths. The lowered incidence of intracranial hemorrhage might in part be attributed to the routine use of vitamin K at the onset of labor, and the fact that pituitary products were never used during the first and second stages of labor. Congenital defects accounted for forty-eight deaths (19.7 per cent). In Bundesen's[1] series in the same city it occurred in only 15.6 per cent. The higher percentage in our series can be accounted for by the lowered total neonatal mortality, which increases the static mortality associated with malformation. Erythroblastosis accounted for less than 3 per cent of these infant deaths.

TABLE VIII. ANATOMIC CAUSES OF DEATH

	1942	1943	1944	1945	1946	1947	TOTAL	PER CENT	
Adrenal hemorrhage	0	0	1	0	0	0	1	0.4	
Bronchopneumonia	2	2	0	0	1	2	7	2.9	
Congenital malformations	8	8	11	5	11	5	48	19.7	
Erythroblastosis fetalis	1	1	0	1	0	3	6	2.4	
Hydrops neonatorum	0	1	0	0	0	0	1	0.4	
Intracranial hemorrhage with tentorial tears	7	5	4	4	3	7	30	12.5	
Lung abscess	0	0	0	0	0	1	1	0.4	
Prematurity	5	10	6	7	11	19	58	23.5	
Prematurity, pulmonary atelectasis	5	8	0	6	3	10	32	13.2	52.9
Prematurity, pulmonary atelectasis, asphyxia	5	1	10	0	14	8	38	16.2	
Persistent thymus, asphyxia	0	0	0	1	1	1	3	1.2	
Undetermined									
no post-mortem	0	1	3	1	1	0	6	2.4	
post-mortem	0	0	0	0	0	1	1	0.4	
Pulmonary atelectasis with asphyxia	0	1	2	1	5	2	11	4.4	
Total	33	38	37	26	50	59	243	100.0	

A Comparative Study of Stillbirth and Neonatal Deaths

These rates were compared with the average of all of the Chicago hospitals and with hospitals throughout the State of Illinois having 1,000 or more births per year. In Table IX, the rates, both neonatal and stillbirth, compare favorably with both city and state institutions.

TABLE IX. COMPARATIVE STUDY (STILLBIRTHS AND NEONATAL DEATHS)

	STILLBIRTHS*			NEONATAL DEATHS†		
	A	B	C	A	B	C
1942	17.8	23.7	xxx	14.1	19.2	xxx
1943	15.9	22.0	20.5	17.6	18.8	19.7
1944	15.0	22.9	20.0	19.3	19.7	22.6
1945	17.8	22.9	20.0	13.2	19.2	23.1
1946	18.2	22.1	18.9	17.5	20.5	23.5
1947	18.3	xxx	16.3	18.0	xxx	22.1

*Per 1,000 total births.
†Per 1,000 live births.
xxx, Not available at time of study.
A, St. Anne's Hospital.
B, Total hospital average, city of Chicago.
C, Total average of hospitals of 1,000 births and over, State of Illinois.

Conclusions

1. A survey of the incidence, etiology, and anatomic manifestations of the conditions producing death of the infant in the early days of life is presented.

2. Prematurity was the sole cause of many deaths in the first few days of life, and was a contributing factor in still others.

3. The reduction in the neonatal mortality rate is in part due to improved prenatal, intrapartum, and premature care.

4. Adequate environment, diet, and nursing care will help preserve life in prematurely born infants.

5. Until we are able to prevent premature labor, this will continue to be the largest contributing factor in the production of neonatal deaths.

6. Early active treatment of the toxemias of pregnancy may prevent the necessity of terminating pregnancy during the early viable period.

7. A more conservative approach to the treatment of placenta previa may lower fetal mortality.

8. A more conservative type of management of breech deliveries might reduce the high mortality in this presentation.

9. Necropsy examinations are necessary to evaluate the causes of infant deaths.

References

1. Bundesen, H. N., and others: J. A. M. A. **111**: 134, 1938.
2. Eastman, N. J.: Am. Pract. **1**: 343, 1946.
3. Hess, J. H., and Lundeen, E. C.: The Premature Infant, Philadelphia, 1941, J. B. Lippincott Company, chap. 1, p. 3.
4. Lull, C. B.: Management of Obstetrical Complications, Philadelphia, 1945, J. B. Lippincott Company, pp. 1-63.
5. McCormick, C. O.: J. Indiana M. A. **31**: 219, 1938.
6. Plass, E. D., and Alvis, H. J.: AM. J. OBST. & GYNEC. **28**: 293, 1934.
7. Potter, Edith L.: J. A. M. A. **124**: 336, 1944.
Sage, Earl C.: J. A. M. A. **124**: 339, 1944.

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Discussion

DR. JAMES E. FITZGERALD.—I may have misunderstood Dr. Hawkins' paper, but I gathered the idea that it might be possible to decrease neonatal mortality by increasing the cesarean section rate. I rather doubt that would be a wise procedure.

To me, the most important thing in the paper was that out of 14,600+ deliveries there were only six deaths from erythroblastosis. I am quite sure that the lay public and some of the medical public have the idea that the death rate from erythroblastosis is rather large and oftentimes enormous. Considering that only 15 per cent were Rh negative, it is still important to remember that there were only six deaths. If this fact were advertised as widely as it should be, this paper would be extremely valuable both to the lay public and to the physician.

DR. EDITH L. POTTER.—I would like to take objection to Dr. Fitzgerald's statement that there has been no decrease in newborn mortality. You will find in some places the neonatal death rate and stillbirth rate are decreasing and that in the last few years something has been done. I would like to present some figures illustrating the general trend of neonatal and stillbirth deaths at The Chicago Lying-in Hospital.

The total mortality from the time the present building was opened in 1931 has decreased for combined stillbirths and neonatal deaths from approximately 41 per 1,000 births to 21 in these seventeen years. When the incidence of neonatal deaths is decreased, stillbirths are also cut down. Anything that leads to the improvement of the state of the mother will lead to improvement in the state of the fetus and of the infant after birth. In our series there has been a decline in both stillbirths and neonatal deaths, stillbirths from 23 to approximately 11 per 1,000 births, and neonatal deaths from 19 to approximately 9.

Only about 5 or 6 per cent of all deliveries are premature, although over half of the deaths after birth were in premature infants. One finds about the same incidence of stillbirths occurring in the premature period as there are infants with the same degree of prematurity succumbing after birth.

The mortality rate for premature infants in 1931 was approximately 28 per cent, i.e., over one-fourth of all premature infants weighing between 1,000 and 2,500 grams died. This has gradually come down—last year it was 13 per cent and for the current year it is 12 per cent. The rate for babies at term (weighing over 2,500 grams) is less than 0.6 per cent.

About 90 per cent of the dead infants and fetuses have been examined at autopsy. The first group includes 28,000 births (1931-1941), the second group 18,000 (1942-1946), the third group slightly over 8,000 (1947-1948). In the first ten-year period birth trauma accounted for 3.4 deaths per 1,000 births. This dropped to 1.0 per 1,000 in the second period, and in the last 8,000 deliveries was responsible for only 0.2 per 1,000 births. Asphyxia decreased from 2.5 per 1,000 to 1.05 per 1,000. Malformations have risen slightly, although they remain practically constant. Erythroblastosis in the last two years accounted for one death in each 1,000 deliveries. Edema of the meninges is something we have been interested in. It is probably included with prematurity in most studies. Babies delivered by cesarean section who subsequently die often show an excessive amount of fluid in the head and present associated pulmonary pathology. This is especially common in premature babies. The majority of premature babies show specific lung changes and we believe the majority die of pulmonary complications. If we can find out how to prevent such pulmonary deaths among premature infants many lives can be saved.

DR. HAWKINS (Closing).—There is only one point on which I would like to defend my position, that is, the question of advocating cesarean section as a means of decreasing neonatal mortality. That is not a personal opinion but is the opinion of certain groups.

ANALYSIS OF FIFTY CASES OF ERYTHROBLASTOSIS FETALIS

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ERYTHROBLASTOSIS fetalis is a disease of the fetal and newborn periods characterized by edema, jaundice, and anemia. The modern concept of its pathogenesis[1] postulates isoimmunization of the maternal organism by a factor (in fetal red cells) which the mother lacks, inherited by the fetus from the father. This substance crosses the placental barrier and causes production of antibodies in sensitized individuals. These antibodies in turn re-enter the fetal circulation and by their effects on the fetal erythropoietic system produce the symptom complex called by Diamond, Blackfan, and Baty[2] erythroblastosis fetalis. The Rh factor is the chief offender although hemolytic disease does occur due to Hr and ABO incompatibility.

In the few years since the discovery of the Rh factor, the description of blocking antibodies[3, 4, 5] and the Coombs test[6, 7] have been of great diagnostic and prognostic importance. The methods of exchange transfusion have been a great aid in treatment. An analysis of fifty cases of erythroblastosis will be presented and an attempt made to establish criteria for the various methods of treatment.

Procedure

1. Rh determination is now required on all pregnant women.
2. An Rh determination is done on husbands of Rh negative women.
3. Rh antibody determinations are done on all Rh-negative mothers; on primiparas at least once, and on multiparas routinely once a month from the seventh month on. In sensitized individuals, antibody titrations are done at least every two weeks. Those who have had previous transfusions are treated as if they had had a pregnancy. If the individual is sensitized, i.e., producing Rh antibodies, her offspring may manifest the clinical findings of erythroblastosis. Titrating the mother's antibodies by testing serial dilutions of her serum against Rh-positive test cells suspended in both saline and 30 per cent bovine albumin indicates how much blocking and/or agglutinating antibody is present. In comparing 20 per cent and 30 per cent bovine albumin as a suspending medium, Levine found reactions stronger with the more concentrated albumin. Another advantage was the elimination of prozones. Our independent observations confirm these findings. There is a correlation, but not a complete one, between the maternal antibody titer and the clinical severity of erythroblastosis in the infant so that in approximately 80 per cent of the cases the manifestations conform with the predictions based on the antenatal tests. A rapidly rising titer during the last trimester of pregnancy is an indication for consideration by the obstetrician of early induction of labor.
4. Careful history of the outcome of previous pregnancies and of previous transfusions will often give valuable clues as to whether hemolytic disease of

the newborn will occur, and how severe it may be. History of previous stillborn or severely jaundiced infants is usually indication that the infant will be severely ill if it is born alive.

5. A Coombs test is done on the red cells in the cord of all babies born of Rh-negative mothers with Rh-positive fathers. A positive reaction indicates that Rh antibody was fixed to the fetal red cells in vivo. This is almost invariably a sign that the newborn will develop clinical erythroblastosis fetalis.

6. Physical examination and blood counts during the first day of life will usually reveal the severe cases. Jaundice or anemia, with or without erythroblastemia, as well as edema, hepatosplenomegaly, and hemorrhagic tendencies are all indications of severe involvement.

Results

With this background, fifty cases of hemolytic disease of the newborn were studied. This represents the number of cases occurring in approximately 11,000 deliveries (Table I). These figures are not entirely reliable for two reasons:

1. Many cases of isoimmunization have been missed because they were not followed in an obstetrical clinic.

2. Mild cases of jaundice or anemia in the nurseries have not been studied as to etiology. Some of these may have had erythroblastosis fetalis.

In our experience one of about 220 newborn babies had erythroblastosis fetalis severe enough to be studied. These figures are somewhat lower than those of some other clinics. The explanation for this is based upon two facts: First, a large proportion of these patients are Negroes. It has been shown by Levine and his associates that 93 per cent of erythroblastosis occurs in Rh-positive offspring of Rh-negative mothers.[8] The incidence of the disease, therefore, varies directly with the percentage of Rh negatives in the population. Negroes are only about 7 per cent Rh negative as compared with 15 per cent of the white population.[9] Second, the tendency toward small families among the private patients in this series makes for a lower incidence.[10]

The general information accumulated is as follows:

1. Rh incompatibility 45 cases
2. ABO incompatibility 5 cases

Twenty-six of the infants were boys and twenty-four were girls. Deaths were evenly divided, seven boys and seven girls. These figures are at variance with statements that morbidity and mortality are more common among male infants.[11] Also, ten of the cases were among Negro infants, the number being roughly proportional to the percentage of Rh-negative individuals in that population.

The cases may be divided into four main groups (Table I):

1. Stillborns, 8 cases (Table II)
2. Treated with multiple transfusions, 23 cases, 6 deaths (Tables III and IV)
3. Treated with exchange transfusion, 11 cases, no deaths (Table V)
4. No therapy, 7 cases, 1 death

In analyzing the stillborn group (Table II) it was found in all cases that the previous obstetrical history was extremely significant. Most of the mothers had had either several jaundiced babies or previous stillborns. Antibody titers varied from 1:32 to 1:512.

At autopsy specific findings referable to erythroblastosis were not always present. If the fetus died early in the last trimester, widespread autolysis associated with maceration prevented adequate histological study. Those that died later in pregnancy showed, in addition to maceration, varying degrees of generalized edema. Increased extramedullary hematopoiesis, particularly in

the liver and spleen, was seen at times. Pronounced jaundice was infrequent. It was impossible to tell whether brain pathology was present because severe post-mortem changes occurred quite uniformly.

TABLE I. CASES DIVIDED ACCORDING TO TYPES OF THERAPY

	NUMBER	AVERAGE MATERNAL RH ANTIBODY TITER	MORTALITY
Stillbirths	8	1:343	8
Treated with multiple transfusions	24	1:70	5
Treated with exchange transfusion	11	1:171	0
No therapy	7	1:135	1
Totals	50	1:145	14

It is questionable whether any of these infants might have survived if labor had been induced during the last month of pregnancy. The problem of induction of labor is twofold. First, there is the obstetrical difficulty of successfully inducing labor with minimum risk to the mother; and, second, procuring an infant mature enough to survive. Examination of the birth weights of the stillborns in our series reveals that despite the fact that some were edematous, only three weighed 5½ pounds or more. It is possible that some of these might have been born alive if labor had been induced earlier.

TABLE II. STILLBIRTHS

MOTHER			INFANT			
CASE NO.	PREVIOUS PREGNANCIES	MATERNAL ANTIBODY TITERS	RACE	SEX	BIRTH WEIGHT	AUTOPSY FINDINGS
1	1 stillborn	Sensitized, no titer	W	F	4 lb. 5 oz.	Macerated Prematurity
7	4 siblings living and well 1 infant died with jaundice	Blocking 1:512	W	F	1 lb. 14 oz.	Macerated No post-mortem
8	1 sibling living and well	Blocking 1:512	W	M	7 lb. 14 oz.	Hydrops with effusion in serous cavities
9	3 siblings living and well	Blocking 1:256 Agg. 1:8	N	F	3 lb. 6 oz.	As above
11	3 siblings living and well	Blocking 1:512 Agg. 1:20	W	M	8 lb. 4 oz.	Hemorrhage into serous cavities Maceration
20	2 siblings living and well 5 stillborn	Blocking 1:64	W	F	4 lb. 15 oz.	Hydrops
26	2 siblings living and well 1 jaundiced 1 stillborn	Blocking 1:32	W	F	4 lb. 3 oz.	Hydrops No post-mortem
32	1 sibling living and well 1 stillborn 1 miscarriage 3 months	Blocking 1:512	W	M	4 lb.	As above

Twenty-two of our cases were handled by watchful waiting and transfusions to correct anemia. Three cases of ABO incompatibility are included in this group; Rh incompatibility accounted for the remainder. Rh antibody titers in these mothers varied from 1:2 to 1:512. Six of these infants died (Tables III and IV).

TABLE III. INFANTS WHO DIED DESPITE MULTIPLE TRANSFUSIONS

MOTHER			INFANT			
CASE	PREVIOUS PREGNANCIES	MATERNAL ANTIBODY TITERS	RACE SEX	BIRTH WEIGHT	COURSE	NECROPSY FINDINGS
14	1 sibling living and well	Blocking 1:64	N-F	5 lb. 10 oz.	Severe jaundice Petechiae R.B.C. 1.08 million Expired 48 hrs.	Jaundice Kernicterus Increased hematopoiesis in liver and spleen
15	2 siblings living and well	Agg. 1:32 Blocking 1:128	W-M	5 lb. 14 oz.	Severe jaundice at birth R.B.C. 1.5 million Permission for treatment denied Expired 48 hrs.	As above plus ulceration of gastrointestinal tract
16	1 sibling living and well	Blocking 1:16	W-M	6 lb. 12 oz.	Jaundice within 24 hrs. Expired 72 hrs.	As above plus interstitial pneumonia bilaterally
28	1 sibling living and well	Agg. 1:32 Blocking 1:128	W-M	5 lb. 5 oz.	Jaundice at birth R.B.C. 4.4 million Expired 80 hrs.	As above
29	1 sibling living and well	Blocking 1:128	W-M	6 lb. 9 oz.	Jaundice and edema at birth R.B.C. 2.8 million Expired 72 hrs.	As above plus fatty infiltration of liver
48	1 sibling living and well	Anti-B 1:512	W-F	—	Jaundice at birth Expired 20 min.	No necropsy

Pathological findings were as follows:

1. Jaundice (present in all cases)
2. Increased hematopoiesis in liver and spleen (present in all cases)
3. Kernicterus (present in four cases)
4. Hemorrhages in skin and viscera (present in four cases)
5. Pulmonary edema and passive congestion (present in one case)
6. Severe interstitial pneumonia (present in one case, no relation to erythroblastosis fetalis)

One infant with erythroblastosis fetalis presumably due to B sensitization died within twenty minutes after birth. In Case 15 (Table III) substitution transfusion was not permitted by the mother despite signs of severe disease within twenty-four hours after birth. In two other instances, the diagnosis was not made until after the appearance of severe clinical signs, because no Rh studies had been done on the mothers during pregnancy. Exchange transfusion was not attempted since it was not felt that the infants could withstand the procedure at the time. The remaining sixteen babies are alive and seemingly well. Most of these were treated before the procedure of exchange transfusion was adopted in our institution. Two of these patients never became clinically jaundiced but developed a gradually increasing anemia which was treated with Rh-negative whole blood transfusions as indicated. Three others became mildly or moderately jaundiced after forty-eight to seventy-two hours. The remainder became icteric within the first twenty-four hours. Icterus persisted for from several days to three weeks. The course was sometimes stormy, complicated by poor feeding ability and secondary infection.

The hospital stay of the infants treated conservatively, without exchange transfusions, varied from seven to thirty-two days. The average hospital stay

was 17.9 days. All were discharged in good condition without physical signs of kernicterus. Follow-up studies have been wanting in some cases; however, none have been readmitted to the hospital for any reason except subsequent anemia.

TABLE IV. INFANTS TREATED WITH MULTIPLE TRANSFUSIONS WHO SURVIVED

MOTHER		INFANT			
CASE NO.	MATERNAL ANTIBODY TITERS	RACE SEX	ONSET OF FINDINGS	NO. OF TRANS-FUSIONS	HOSPITAL STAY (DAYS)
3	Blocking 1:64	N-M	Jaundice at birth R.B.C. 3.5 million	4	31
5	Blocking 1:32	W-M	Jaundice 24 hrs. R.B.C. 1.5 million	8	31
6*	Sensitized No titer	W-F	Jaundice 72 hrs. R.B.C. 3 million on 4th day	1	8
12*	Blocking 1:16 Agg. 1:4	W-F	Jaundice 24 hrs. R.B.C. 2.75 million on 6th day	4	25
18	Blocking 1:64	W-F	Jaundice 4 hrs. R.B.C. 4.5 million	5	33
19*	Blocking 1:512 Agg. 1:16	W-M	Pallor R.B.C. 1.2 million on 5th day	8	31
25	Blocking 1:16	N-M	Jaundice 24 hrs. R.B.C. 4.1 million	4	22
27	Blocking 1:4	W-M	Jaundice 24 hrs. R.B.C. 3.7 million	1	8
31	Blocking 1:8	W-F	Pallor 72 hrs. R.B.C. 1.8 million	3	14
34	Agg. 1:2	W-F	Jaundice 48 hrs. R.B.C. 4.5 million	2	10
35	Anti-B 1:256	W-F	Jaundice at birth R.B.C. 3.5 million	1	18
36	Sensitized No titer	W-M	Pallor 4th day R.B.C. 2.1 million	4	17
39	Blocking 1:16 Agg. 1:4	W-M	Jaundice 24 hrs. R.B.C. 3.6 million	5	19
41	Blocking 1:32	W-M	Jaundice 24 hrs. R.B.C. 5 million	2	10
43	Anti-A 1:128	W-M	Jaundice 24 hrs. R.B.C. 4.5 million	1	16

*Transferred from other hospitals to Kings County Hospital.

A total of eleven cases have been treated by exchange transfusion (Table V). Maternal antibody titers in this group ranged from 1:16 to 1:512. One case was apparently due to O-B incompatibility with respect to the agglutinogen B. All cases of Rh incompatibility had positive Coombs tests; and all showed early clinical evidence of erythroblastosis fetalis. The first three exchange transfusions were done by the saphenous vein—radial artery[12, 13] technique on the pediatrics ward of the hospital. They required long periods of hospitalization chiefly because they developed secondary infections on the pediatric wards. The remainder were done via plastic catheter inserted in the umbilical vein.[14] Therapy included the use of calcium gluconate for replacement of calcium and penicillin for prevention of sepsis. These transfusions were done in an operating room on the obstetrical floor. The infant was then followed in the regular newborn nursery. In our limited experience this has shortened the hospital stay considerably.

There were no deaths in this group. In all cases the procedure was done within the first twenty-four hours. The infants usually had a smooth recovery. Blood counts, with three exceptions, remained within normal limits. Jaundice

disappeared rapidly and discharge from the hospital was accomplished reasonably quickly. The average hospital stay of the last eight babies (transfused via the umbilical vein) was only 8.7 days. It is interesting to note (Table V) that while four of these mothers had had previous stillborns, their infants, treated with exchange transfusion, survived.

TABLE V. TREATED WITH EXCHANGE TRANSFUSION

MOTHER			INFANT				
CASE NO.	PREVIOUS PREGNANCIES	MATERNAL ANTIBODY TITERS	RACE SEX	COOMBS TEST ON CORD CELLS	ONSET OF FINDINGS	AGE TIME OF THERAPY	HOSPITAL STAY (DAYS)
2*	5 siblings living and well	Blocking 1:256	W-M	Not done	Jaundice at birth R.B.C. 1.75 million	Within 12 hrs.	60
4*	1 sibling living and well 2 jaundiced 1 stillborn	Blocking 1:32	W-M	Not done	Jaundice at birth R.B.C. 3 million	Within 12 hrs.	21
10*	5 siblings living and well 1 stillborn	Blocking 1:512 Agg. 1:4	W-M	4 plus	Jaundice in 3 hrs. R.B.C. 3.6 million	4 hrs.	45
22	3 siblings living and well 2 stillborn	Blocking 1:512	W-M	4 plus	Jaundice at birth R.B.C. 3.5 million	2 hrs.	9
23	8 siblings living and well 1 stillborn	Blocking 1:128	W-M	2 plus	Jaundice 2 hrs. R.B.C. 4.1 million	3 hrs.	14
24	First pregnancy	Anti B 1:128	N-F	Negative	Jaundice in 24 hrs. R.B.C. 2.9 million	24 hrs.	9
30	1 sibling living and well	Blocking 1:16	W-F	3 plus	Jaundice 3 hrs. R.B.C. 3.8 million	6 hrs.	10
33	1 sibling living and well	Blocking 1:64	W-M	4 plus	Jaundice 12 hrs. R.B.C. 6 million	16 hrs.	6
37	2 siblings living and well	Agg. 1:128 Blocking 1:128	N-M	4 plus	Jaundice 3 hrs. R.B.C. 4.7 million	3 hrs.	6
45	5 siblings living and well 3 jaundiced	Blocking 1:32	W-M	4 plus	Jaundice at birth R.B.C. 3.9 million	½ hr.	7
47	6 siblings living and well 3 jaundiced	Blocking 1:64	W-F	4 plus	Jaundice at birth R.B.C. 3.5 million	1 hr.	7

*Saphenous vein-radial artery technique. Remainder treated via plastic catheter in umbilical vein.

Discussion

The success of the present treatment depends upon a three-man team—the obstetrician, pediatrician, and immunohematologist. Close cooperation and special laboratory techniques have aided in detecting the mothers who may give birth to affected offspring. The ultimate decision as to mode of therapy is based on all the facts that can be accumulated without relying completely on any single finding.

1. *History.*—A history of previous stillborns, jaundiced babies, or previous transfusions should place one on guard regarding the possibility of isoimmunization and impending severe disease.

2. *Maternal Antibody Titers.*—In general, a rising maternal Rh antibody titer is an indication that the infant may have hemolytic disease. The severity of the disease conformed with the titer of antibodies in the mother's serum about 80 per cent of the time. Therefore, except when the titers are extremely high or very low, the titer values are not a dependable indication of the severity of the manifestations in the unborn child. The titer sometimes rises rapidly during the last month of pregnancy, and occasionally in a nonspecific manner when the fetus is Rh negative. Therefore, the tendency is to induce labor when the obstetrician feels that the fetus will not be excessively premature. From our study of the stillborn group, we feel that, in these cases, induction of labor would have produced very few live mature infants.

3. *Clinical and Laboratory Findings in the Infant.*—Jaundice, edema, anemia, hepatosplenomegaly, and bleeding tendencies present at birth or soon thereafter are indications of severe erythroblastosis and correspondingly serious prognosis. Anemia and/or erythroblastomia usually mean that hemolysis has occurred. A positive Coombs test is an indication that the infant has Rh antibody fixed to the red blood cell. However, there is not a complete correlation between degree of coating of the cord cells and the severity of clinical manifestations.

If all the above diagnostic aids are properly utilized, diagnosis of erythroblastosis is rarely difficult. Clinically, congenital syphilis, sepsis, diabetes, and hemorrhage due to birth injury can closely simulate hemolytic disease of the newborn. Jaundice, anemia, edema, hepatosplenomegaly, petechial hemorrhages, and erythroblastemia can occur in all of the above conditions. In these cases we are largely dependent upon the laboratory for our diagnosis.

The ultimate decision as to therapy can usually be made only after the birth of the baby. This can be done by weighing the clinical and laboratory evidence found in the infant.

Success in the treatment of erythroblastosis depends upon early detection of antibodies in the maternal serum. At the time of delivery, the hematologist and pediatrician should both be present to determine what should be done. Since the modern concept of this disease has been accepted, almost all observers advocate the use of Rh-negative red blood cells in the treatment of this disease. In this series, Rh-negative whole blood was used exclusively when the Rh factor was the isoimmunizing agent.

It is our feeling that substitution transfusion is the treatment of choice in all cases where clinical evidence of erythroblastosis is found at birth or within the first twenty-four hours. When the cord cells reveal a positive Coombs test and there is no other evidence of erythroblastosis, the infants must be watched carefully for jaundice and evidence of anemia during the first twenty-four hours. If jaundice, anemia, or increasing erythroblastemia occurs within this period, exchange transfusion should be done promptly. Infants who do not show any clinical evidence within the first twenty-four hours can usually be treated conservatively.

The advantages of exchange transfusion over expectant treatment are as follows[15, 16]:

1. Removal of large amounts of antibody.

2. Removal of a large volume of coated cells and their replacement with normal Rh-negative cells which are resistant to the antibody and will have a normal survival time in the circulation. This results in the elimination of hemolysis. Whether exchange transfusion affects the incidence of liver damage or kernicterus is still an unanswered question. This series is too small for any

valid conclusions, but kernicterus has not yet been seen in any of these cases where early exchange transfusion was done. Most observers agree with this though a few seem to feel that brain damage is the result of damage done in utero.

3. Prevention of overloading of the circulation.

4. Elimination of numerous blood counts and transfusions. This shortens the period of hospitalization, thereby cutting down exposure to infections on the ward.

5. The use of the catheter in the umbilical vein seems to be the method of choice for the following reasons:

A. Passage of the catheter is easy, and more rapid than cutting down on veins and arteries.
B. There is no scarring when using the catheter.
C. This procedure can be done if necessary with the infant in a heated crib under oxygen therapy with a minimum of handling.
D. No heparin is required to facilitate bleeding.
E. No arteries need be tied off when the exchange transfusion is terminated.

The disadvantages of exchange transfusions:

1. In the procedure using the radial artery[17] and saphenous vein, heparin is usually used, though the procedure has been done without heparin. The use of heparin[18] has been condemned by Wallerstein and Diamond on the grounds that the hemorrhagic tendency sometimes present in erythroblastosis may be increased. However, Wiener asserts that the heparin used does no harm, and is largely washed out during the exchange. In our experience with three cases using heparin, no evidence of untoward bleeding was encountered.

2. Air embolus.[19]

3. Hemorrhage into the peritoneal cavity.

4. Liver necrosis. Rosenblatt[20] has reported three cases of liver necrosis in children who had received exchange transfusion. He stated that the etiology might be due to the citrate in the blood. According to Wiener, liver necrosis was merely part of the damage caused by the disease. In support of this, are reports of cases in the literature untreated or treated only with small transfusions which showed similar liver damage.

We have encountered none of the above complications in our series of exchange transfusions.

Prophylaxis of erythroblastosis fetalis by neutralization of maternal antibodies during the last trimester of pregnancy would be ideal. Carter[21] has reported separating a lipoid extract, chemically resembling cholesterol from Rh-positive red blood cells. Goldsmith[22] has used this material in three strongly sensitized women with good results. Attempts by ourselves and others to reproduce Carter's work have been, thus far, unsuccessful. Personal communications with Wiener,[23] Unger,[24] and Levine[25] have revealed that they, too, have thus far been unable to duplicate Carter's findings.

Until neutralization of maternal antibodies becomes a definitely feasible procedure we shall be obliged to handle the problems of erythroblastosis with the means at hand. The ultimate decision as to mode of therapy, either conservatively or by exchange transfusion, depends upon all the facts that can be accumulated.

Summary and Conclusions

1. Fifty cases of erythroblastosis fetalis are presented.

2. At present successful handling of cases of erythroblastosis depends to

a large extent on the prenatal knowledge that the offspring may be affected. Past obstetrical history and maternal antibody determinations are essential data in every pregnancy.

3. Decision as to mode of therapy usually cannot be made until after birth of the infant. Then, all of the evidence, laboratory and clinical, must be evaluated before exchange transfusion or a more conservative course is undertaken.

4. Exchange transfusion is, at present, the most effective way to treat severe erythroblastosis fetalis. The method of choice is by plastic catheter via the umbilical cord.

References

1. Levine, P.: J. Pediat. **23**: 656, 1943.
2. Diamond, L. K., Blackfan, K. D., and Baty, J. M.: J. Pediat. **1**: 268, 1932.
3. Wiener, A. S.: Proc. Soc. Exper. Biol. & Med. **56**: 173, 1944.
4. Race, R. R.: Nature **153**: 771, 1944.
5. Diamond, L. K., and Abelson, N. M.: J. Clin. Investigation **24**: 122, 1945.
6. Coombs, R. R. A., Mourant, A. E., and Race, R. R.: Brit. J. Exper. Path. **26**: 255, 1945.
7. Coombs, R. R. A., Mourant, A. E., and Race, R. R.: Lancet **1**: 264, 1946.
8. Levine, P., Vogel, P., Katzen, E. M., and Burnham, L.: Science **94**: 371, 1941.
9. Wiener, A. S., Belkin, R. B., and Sonn, E. B.: Am. J. Phys. Anthropol. **2**: 187, 1944.
10. Levine, P.: Blood. Special Issue No. 2, p. 3, January, 1948.
11. Halperin, J., Jacobi, M., and Dubin, A.: Am. J. Obst. & Gynec. **50**: 326, 1945.
12. Wiener, A. S., Wexler, I. B., and Gamera, E.: Am. J. Dis. Child. **68**: 317, 1944.
13. Polayes, S., quoted by Wallerstein: Am. J. Dis. Child. **73**: 19, 1947.
14. Diamond, L. K., quoted by Wallerstein: Blood. Special Issue No. 2, p. 170, 1948.
15. Wallerstein, H.: Blood. Special Issue No. 2, p. 170, 1948.
16. Diamond, L. K.: Pediatrics **2**: 250, 1948.
17. Wiener, A. S., and Wexler, I. B.: J. Lab. & Clin. Med. **31**: 1015, 1946.
18. Wallerstein, H.: Proc. Amer. Assoc. of Blood Banks, page 24, August, 1948.
19. Wiener, A. S., and Wexler, I. B.: Blood **4**: 1, 1949.
20. Rosenblatt, P.: Am. J. Clin. Path. **18**: 700, 1948.
21. Carter, B. B.: Am. J. Clin. Path. **17**: 646, 1947.
22. Goldsmith, J. W.: Bull. Univ. Minnesota Hosps. **20**: 188, 1948.
23. Wiener, A. S.: Personal communication.
24. Unger, L.: Personal Communication.
25. Levine, P.: Personal Communication.

Da Cunha, Pedro: Toxemia in the Second Half of Pregnancy at the Lying-In Hospital "Dr. Alfredo Costa" (Lisbon), in the Years 1943-1948, An. brasil. de ginec. **26**: 251, 1948.

From a series of 17,187 patients delivered in the five years, 1943 to 1948, the author reports 108 cases of pre-eclampsia and 76 cases of eclampsia. There was no prenatal care in the last group. Sixty-eight of the seventy-six eclampsia patients were primiparous while sixty-four developed convulsions in the intrapartum period. The incidence was higher in the winter months. Magnesium sulphate and 40 per cent glucose were the standard treatment. Maternal deaths occurred in five cases, or 7.3 per cent, and a fetal mortality of 17.4 per cent.

C. E. Folsome.

CLINICAL EVALUATION OF METHERGINE

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METHERGINE, a new synthetically prepared drug having oxytocic properties, has been recently introduced. It was first prepared by Stoll and Hofmann[1] from lysergic acid to form d-lysergic acid-dl-hydroxybutylamide-2. The pharmacology has been studied by Rothlin[2] and Kirchhof and co-workers,[3, 4] who demonstrated the oxytocic effect, an epinephrine-like action upon the gut, lack of sympathicolytic action and absence of hyperpyrexia and mydriasis when therapeutic doses are administered.

The importance of a safe, effective synthetically prepared oxytocic becomes apparent when the scarcity of crude ergot, rich in alkaloidal content, is considered, as well as the uncertain supply or total lack of ergot during times of war.

Previous reports have considered the drug in relation to time of action, blood loss, lochia, and length of hospitalization[5]; have compared the blood loss and length of the third stage with intravenous and intramuscular administration of the drug,[6] and have studied the blood loss and length of the third stage when the drug was given after delivery of the placenta and at delivery of the shoulders.[7] Others[8-15] have shown that the drug compares favorably with the oxytocic action of ergonovine in respect to time of action, blood loss, and length of third stage.

Material

The present study was undertaken to evaluate Methergine in comparison with ergonovine in a fairly large series of cases. The analysis considers such factors as parity of patients, type of delivery, anesthetic, time of action of the drug, and blood loss. In all cases the blood loss was estimated. The inaccuracy of estimation is appreciated but the estimates for both the Methergine and ergonovine groups were made by the same obstetricians, so that errors of estimation are the same for both groups. A comparison of blood loss, not an absolute measurement, was considered to be of prime importance in this study. The only selectivity used in choosing the cases was that in all instances the drugs were given intravenously at the birth of the shoulders in cephalic presentations and at the birth of the buttocks in breech presentations, that all required data were completely recorded, and that no cases delivered by cesarean section were included. The series consists of 550 patients who received Methergine* (0.2 mg. in 1 c.c.) and a control group of 406 who were given ergonovine. It is believed that the series is large enough to reach valid conclusions. The majority were private patients of several of the staff members, to whom our appreciation is expressed for their co-operation in this study. Other patients were those from the hospital clinic and from the service at St. Ann's Maternity Hospital.

*Supplied by Sandoz Pharmaceuticals, San Francisco, California.

For both the Methergine and the ergonovine groups, over 80 per cent of the patients were gravida i and ii (Table I).

TABLE I. NUMBER OF PATIENTS

GRAVIDA	METHERGINE	ERGONOVINE
i	310	199
ii	142	127
iii	60	50
iv	26	17
v	4	7
vi	6	4
vii	2	2
	550	406

In the Methergine group, 187, or 34.0 per cent, were delivered spontaneously and 336, or 61.09 per cent, by low forceps. There were twelve breeches (2.18 per cent) of which two were delivered spontaneously, six were breech extractions, two had manual aid, and two had forceps to the aftercoming head. Included in the remainder were Kjelland's forceps, Scanzoni maneuver and 2 midforceps operations. Of the ergonovine group, there were 186 or 45.81 per cent spontaneous deliveries, 205 or 50.49 per cent low forceps and 8 breeches (1.97 per cent) of which 4 were spontaneous, 2 were extracted and 2 had forceps to the aftercoming head (Table II).

TABLE II. NUMBER OF PATIENTS

METHOD OF DELIVERY	METHERGINE	ERGONOVINE
Spontaneous	187 (34 %)	186 (45.81%)
Low forceps	336 (61.09%)	205 (50.49%)
Breech	12 (2.18%)	8 (1.97%)
Others	15 (2.73%)	7 (1.73%)

Low spinal anesthesia was used for 348, or 63.27 per cent, of the Methergine cases, nitrous oxide-oxygen-ether for 128, or 23.27 per cent, ether for 62, or 11.27 per cent, nitrous oxide-oxygen for ten and predendal block for two. Nitrous oxide-oxygen-ether was used for 229, or 56.41 per cent, of the ergonovine cases, spinal for 169, or 41.62 per cent, ether for four cases and nitrous oxide-oxygen and pudendal block for two each.

For both groups, the time was determined from the injection of the drug until the first contraction of the uterus and from injection until the placenta was delivered. In both groups the shortest time from injection to first contraction was 0.5 minutes and the longest time was 7.0 minutes. With Methergine, 89.63 per cent of patients had the first contraction in 2 minutes or less and with ergonovine 94.82 per cent had the first contraction in 2 minutes or less. The placenta was delivered within 5 minutes or less in 87.27 per cent of the Methergine group and in 80.54 per cent of the ergonovine group. Fig. 1 illustrates these two time factors for both groups. With Methergine there were four patients who had the placenta removed manually, at 13, 16, 18, and 20 minutes from the time of injection. These were all cases of abruptio placentae or placenta previa. With ergonovine there were two manual removals of the placenta, one at 13 minutes for placenta previa and one at 40 minutes, for retained placenta.

Blood Loss

It is again emphasized that the inaccuracy of estimated blood loss is appreciated, but that the same degree of error existed in the two groups studied

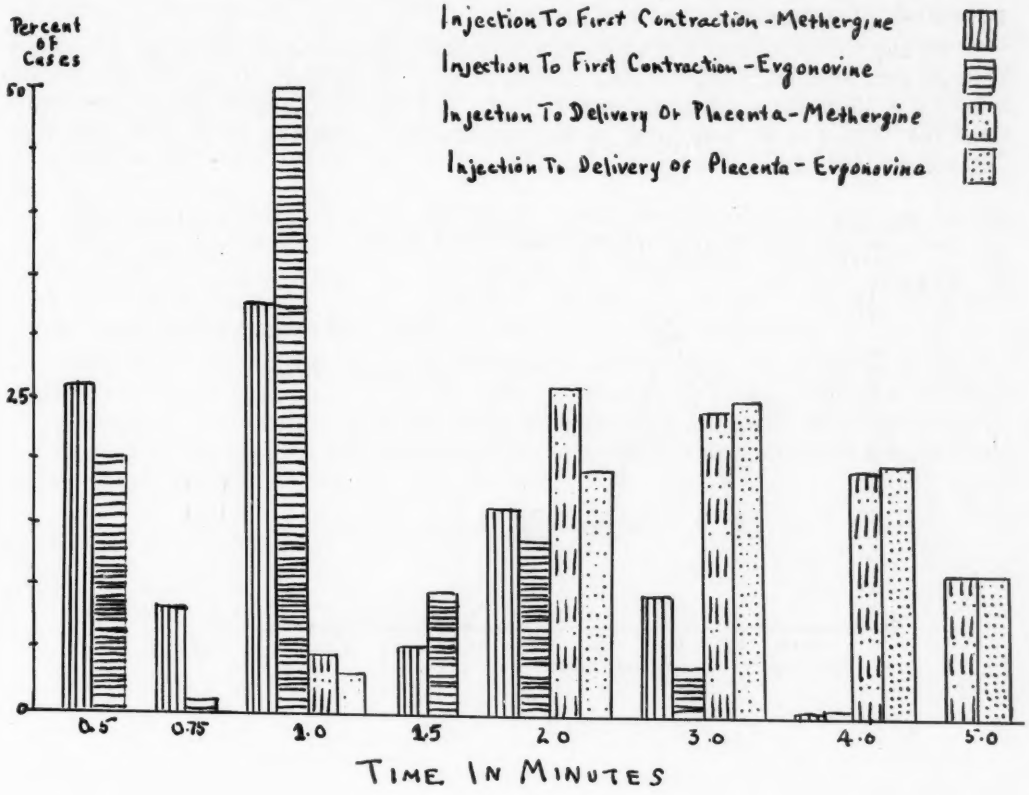
Percent of Cases
50
25
0
Injection To First Contraction - Methergine
Injection To First Contraction - Ergonovine
Injection To Delivery Of Placenta - Methergine
Injection To Delivery of Placenta - Ergonovine
0.5
0.75
1.0
1.5
2.0
3.0
4.0
5.0
TIME IN MINUTES

Fig. 1.

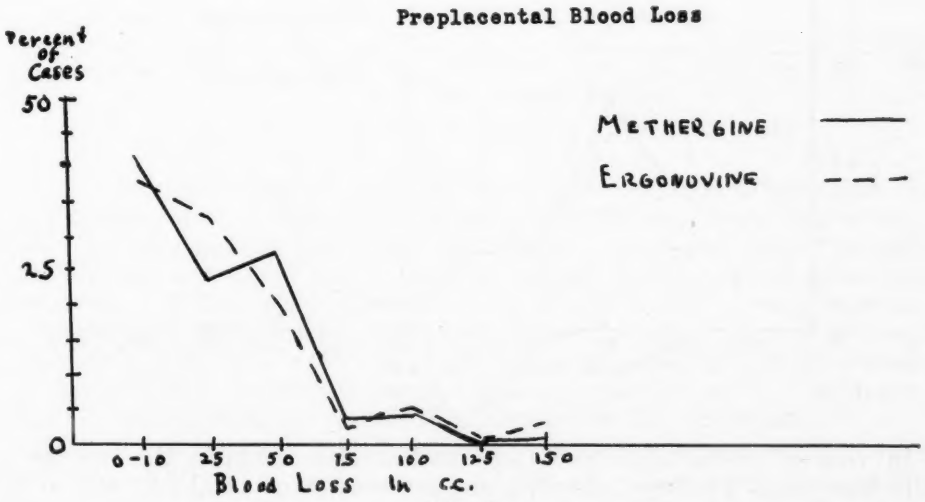
Preplacental Blood Loss
Percent of Cases
50
25
0
METHERGINE
ERGONOVINE
0-10
25
50
75
100
125
150
Blood Loss In cc.

Fig. 2.

and that the primary interest was in a comparison between the two groups. Blood loss for each drug was considered from the standpoints of preplacental, placental, postplacental, and total losses.

In the preplacental category, the average loss when Methergine was used was 26 c.c., and with ergonovine it was 30 c.c. With both drugs the minimum was 0 c.c. and the maximum was 150 c.c. Of the Methergine group, 98.9 per cent lost 100 c.c. or less, and of the ergonovine patients, 97.75 per cent lost 100 c.c. or less.

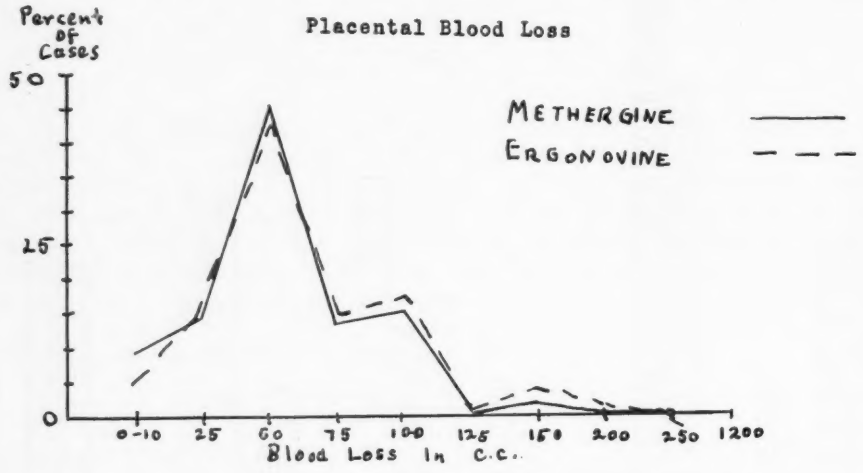

Fig. 3.

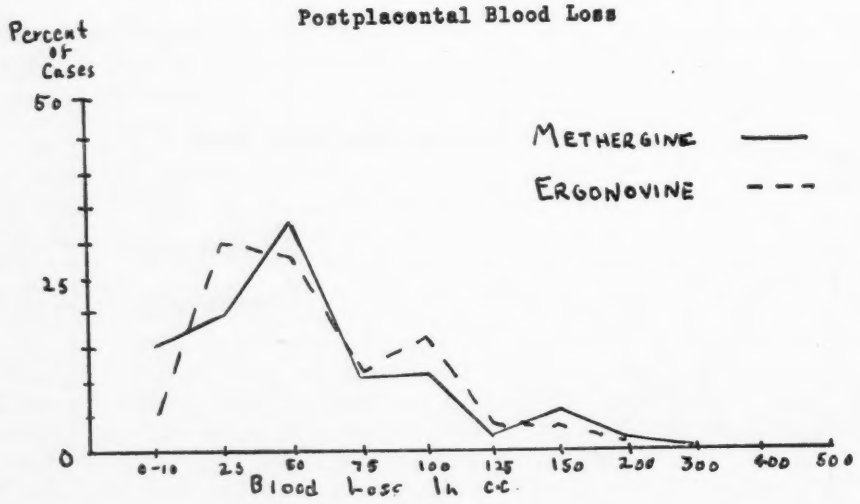

Fig. 4.

In view of the inequality of the number of patients in the two groups, charts have been prepared showing the percentage of total patients of each group in relation to the amount of blood lost. A more accurate graphic comparison can be given in this way, rather than by showing absolute numbers of patients for the several blood loss amounts.

The placental blood loss for the Methergine series averaged 58 c.c., and varied from a minimum of 0 c.c. to a maximum of 1,200 c.c., with 99.0 per cent of patients losing 150 c.c. or less. There was one case of postpartum hemorrhage (over 500 c.c.). In this case there was a partial separation of the placenta. If this case is excluded, the average blood loss becomes 56 c.c. For ergonovine the average loss was 62 c.c., the minimum 0 c.c., and the maximum 250 c.c., with 98.3 per cent losing 150 c.c. or less. Fig. 3 graphically presents the comparison of "placental" blood loss of the Methergine and ergonovine groups.

Postplacental blood loss in the Methergine group varied from 0 c.c. to 500 c.c. The average loss was 56 c.c., and 98 per cent of the patients lost 200 c.c. or less. With ergonovine, the loss ranged from 0 c.c. to 400 c.c., average 62 c.c., and 98.76 per cent of the patients lost 200 c.c. or less. There were two patients of the Methergine group who lost approximately 500 c.c.

Fig. 4 graphically shows the comparison of the amounts of blood lost after delivery of the placenta, using the two different oxytocics. Of the patients who received Methergine, who lost more than 350 c.c. of blood, one lost 400 c.c., and two lost 500 c.c. In the ergonovine group, two patients lost 225 c.c., two lost 300 c.c. and one lost 400 c.c.

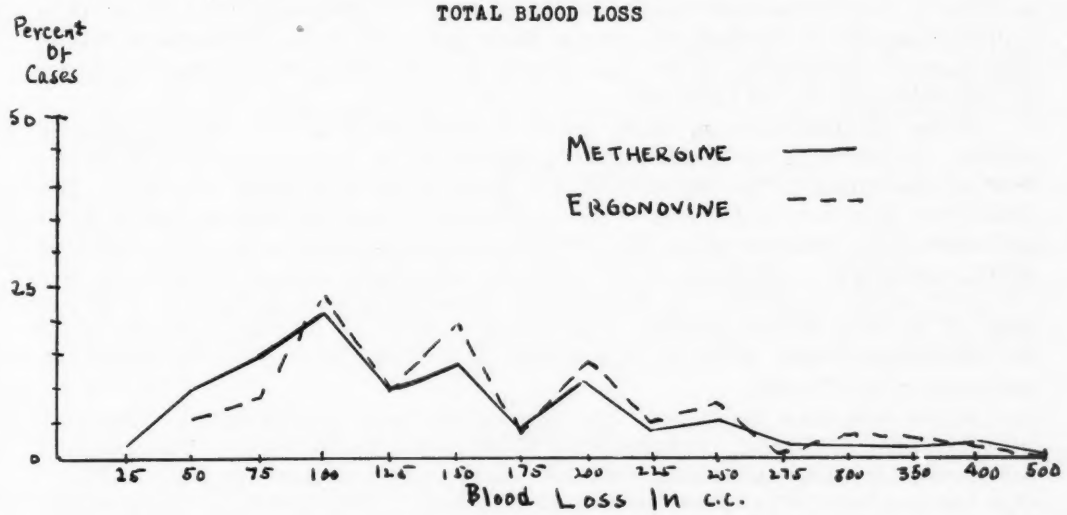

Fig. 5.

The total blood loss of the patients who were given Methergine varied from a minimum of 25 c.c. to a maximum of 2,000 c.c., with an average loss of 149 c.c. One patient had a loss of 2,000 c.c., the same patient whose placental blood loss was 1,200 c.c., the hemorrhage due to partial separation of the placenta. If this case is excluded, the average total blood loss becomes 145 c.c. There were three patients, 0.54 per cent of the total, who had postpartum hemorrhages, using the standard of blood loss in excess of 500 c.c. considered to be hemorrhage. Of those, one lost 550 c.c., one lost 600 c.c., and one lost 2,000 c.c. Ninety-eight per cent of the patients lost 200 c.c. or less.

Total blood loss for the ergonovine patients averaged 146 c.c. ranging from a low of 50 c.c. to the maximum of 500 c.c. There were no postpartum hemorrhages in this group, and 99.27 per cent had a total blood loss of 400 c.c. or less.

Fig. 5 shows the comparison of total blood loss of the two groups.

Summary

A fairly large series of cases has been studied in an effort to determine the efficacy of Methergine, a newly introduced synthesized oxytocic drug. There were 550 patients who received Methergine, and a control group of 406 patients who were treated according to the current routine of intravenous ergonovine.

In both groups, slightly over 80 per cent of the patients were either primigravidas or secundigravidas.

The method of delivery of the patients who were given Methergine was spontaneous in 34 per cent of the cases and by low forceps in 61.09 per cent. Various types of breech delivery accounted for 2.18 per cent of the cases. In this study, all cesarean sections were excluded. Delivery of the ergonovine patients was spontaneous in 45.81 per cent of the cases, by low forceps in 50.49 per cent, and either spontaneous delivery or extraction of the breech in 1.97 per cent.

Spinal anesthesia was used for 63.27 per cent of the Methergine group, nitrous oxide-oxygen-ether for 23.27 per cent, and ether for 11.27 per cent. There were a few cases delivered under nitrous oxide or local block anesthesia. Only 41.62 per cent of the ergonovine patients were delivered under spinal anesthesia, while the incidence of nitrous oxide-oxygen-ether was more than double that of the Methergine group, 56.41 per cent of the patients receiving this type of anesthetic. Ether was rarely used in this group, being employed in only 0.98 per cent of the cases.

When Methergine was used, the first contraction of the uterus occurred within two minutes or less from the time the drug was injected in 89.63 per cent of the cases. For ergonovine, the percentage was 94.82 per cent. The time from injection to the end of the third stage was 5 minutes or less in 87.27 per cent of the patients given Methergine, and in 80.54 per cent of the patients given ergonovine. Manual removal of the placenta was performed on 0.72 per cent of the patients who were given Methergine as compared to 0.49 per cent of the ergonovine patients. The total number of manual removals, four for Methergine and two for ergonovine, is so small that any statistical importance is questioned.

Blood loss was considered in four categories: preplacental, placental, postplacental, and total. Preplacental blood loss with Methergine ranged from a minimum of 0 c.c. to a maximum of 150 c.c. with an average loss of 26 c.c. One hundred cubic centimeters or less was lost in 98.9 per cent of the cases. With ergonovine, the minimum loss was 0 c.c., the maximum 150 c.c., the average loss 30 c.c. and 97.75 per cent of the patients lost 100 c.c. or less.

With Methergine, the minimum placental blood loss was 0 c.c. The maximum loss was 1,200 c.c., in a case of partial separation of the placenta. All of the others had a loss of 250 c.c. or less, with an average of 58 c.c., and 99 per cent had a loss of 150 c.c. or less. Minimum loss with ergonovine was 0 c.c., maximum was 250 c.c., average loss was 62 c.c., and 98.3 per cent lost 150 c.c. or less.

Postplacental blood loss with Methergine varied from a minimum of 0 c.c. to a maximum of 500 c.c. The average loss was 56 c.c. with 98 per cent losing 200 c.c. or less. With ergonovine the minimum loss was also 0 c.c., the maximum was 400 c.c., the average loss was 62 c.c., and 98.7 per cent lost 200 c.c. or less.

Minimum total blood loss with Methergine was 25 c.c. The patient who had a placental blood loss of 1,200 c.c. lost a total of 2,000 c.c. Of the other cases, the total loss was 600 c.c. or less. Average loss for all cases was 149

c.c., with 98 per cent of patients losing 200 c.c. or less. With ergonovine the minimum loss was 50 c.c. and the maximum was 500 c.c. The average loss was 146 c.c., with 99.2 per cent of patients losing 200 c.c. or less.

Conclusions

Methergine has been shown to be an effective oxytocic drug as judged by:

1. Prompt uterine contraction
2. Short third stage of labor
3. Satisfactory postpartum blood loss

As compared to the controls, there was no difference of statistical significance in the time from injection of the drug to either first contraction of the uterus or end of the third stage. Although there was considerable difference in the percentage incidence of manual removal of the placenta (0.72 per cent for Methergine, 0.49 per cent for ergonovine) the number of cases for each drug is so small that valid conclusions cannot be drawn.

In the four categories of blood loss, preplacental, placental, postplacental, and total, there was no statistically significant difference. Study of the blood loss curves reveals a remarkable parallelism for the two drugs.

Unfortunately, the study did not include an evaluation of changes in blood pressure with the two drugs. Although some epinephrine-like effect upon the gut has been demonstrated,[3] there seems to be no vasopressor action of Methergine.

None of the patients showed any sensitivity to Methergine and there were no undesirable side effects.

The study indicates that Methergine is a safe, potent oxytocic drug, that corresponds in several details of its action with ergonovine. Of great significance is the fact that Methergine is partially synthetic, which may become of great importance if the usual supply of potent crude ergot is curtailed or interdicted.

References

1. Stoll, A., and Hofmann, A.: U.S. Patents, Numbers 2,265,207 and 2,265,217.
2. Rothlin, E.: International Monthly Review of Obst. and Gyn. **122**: 1946.
3. Kirchhof, A. C., Racely, C. A., Wilson, W. M., and David, N. A.: West. J. Surg. **52**: 197, 1944.
4. Kirchhof, A. C., David, N. A., Phatak, N. M., and Racely, C. A.: J. Am. Pharm. A. (Scient. Ed.) **36**: 145, 1947.
5. Tollefson, D. G.: West. J. Surg. **52**: 383, 1944.
6. Tritsch, J. E., and Schneider, E.: Am. J. Obst. & Gynec. **50**: 434, 1945.
7. Baskin, M. J., Harvey, E. L., and McEndaffer, D M.: Rocky Mountain M. J. **44**: 208, 1947.
8. Roberts, P. C.: West. J. Surg. **52**: 380, 1944.
9. Brougher, J. C.: West. J. Surg. **53**: 276, 1945.
10. Cartwright, E. W., and Rogers, W. C.: West. J. Surg. **54**: 59, 1946.
11. Bunch, J. R.: Rocky Mountain M. J. 1948.
12. Williams, Ben C.: Rocky Mountain M. J. **44**: 207, 1947.
13. Gill, R. C. J.: Obst. & Gynaec. Brit. Emp. **54**: 482, 1947.
14. Gipstein, B. L.: Am. J. Obst. & Gynec. **54**: 1065, 1947.
15. Tritsch, J. E., Schneider, E., and Longworth, E. F.: New York State J. Med. **48**: 293, 1948.

PRIMARY UTERINE MALIGNANCY

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CARCINOMA of the uterus is second only to carcinoma of the breast as the most common malignancy in women. If the survival rates for individuals having these lesions could be increased, the deaths in women caused by malignancy would be greatly reduced. Periodically, one should analyze the results obtained from the treatment employed and compare these results with those reported from other sources in order to determine whether changes in therapy should be made. Most of the reports regarding the end results in the treatment of carcinoma of the uterus are from the larger centers of medical treatment. However, a large proportion of the patients with this disease are treated at smaller institutions.

Material

With this thought in mind, this analysis was made. It covers a twelve-year period, 1935 to 1946 inclusive, at The Brooklyn Hospital. This report is also a continuation of the appraisal of our results first reported by W. S. Smith in 1935, covering the period 1920 to 1929, inclusive, and again in 1940 by the senior author of this paper, covering the period 1930 to 1934, inclusive. The five-year survival rates in those first two reports were very poor, being only 12 and 14 per cent, respectively, for carcinoma of the cervix. Several changes in therapy have been made between those reports and the present one. The better results reported in this series are gratifying and justify these changes.

There were 189 cases included in this study and they were divided almost equally between malignancy of the cervix and of the corpus. Ninety-eight were cervical and 91, corporeal. The ratio of cervical carcinoma to cancer of the endometrium is usually given as 3:1. A further breakdown of our series was thus indicated. It was found that the above ratio occurred in the ward patients, but in the private patients 62 per cent had involvement of the corpus, a ratio of almost 1:2 (Table I). This finding was also observed by Corscaden and Gusberg who reported twice as many private patients in the corpus group as in the cervical cases.

We have no adequate explanation for this reversal, but it has been suggested that a larger percentage of private than of clinic patients return for postpartum checkups. Therefore, benign cervical lesions such as erosions and inflammatory processes are treated, and the possibility of the development of malignancy from them is removed. It would be advisable for future reports from other institutions to include this information. It would then be possible to determine if this finding is generally true.

The ages of the patients in this series followed the generally accepted distribution (Table II). The great majority of the patients in both the cervical and corporeal groups were between 40 and 59 years. However, there were many more patients with cervical cancer than with corporeal cancer below the age of 40, whereas the reverse was found to be true among patients over 60 years of age. The youngest patient in the cervical group was 25 and the oldest, 72. In the corporeal group, the youngest patient was 30 and the oldest, 76. There were ten patients, or 5.3 per cent, in the entire series who were Negroes.

TABLE I. DISTRIBUTION OF PATIENTS

	CERVIX		CORPUS	
	NUMBER OF CASES	PERCENTAGE	NUMBER OF CASES	PERCENTAGE
Ward	51	52.4	15	16.5
Private	47	47.6	76	83.5
Total	98	100	91	100

TABLE II. AGE INCIDENCE

AGE GROUP	CERVIX	CORPUS
20-29	3	0
30-39	16	5
40-49	26	23
50-59	35	35
60-69	17	21
70-79	1	7
Total	98	91
In the above age groups:		
Youngest patient	25	30
Oldest patient	72	76

Of the total of 189 patients, 10 (5.3 per cent) were Negro, the others, white.

The symptom which usually caused the patients to seek medical advice was abnormal vaginal bleeding which manifested itself in several forms (Table III). Postmenopausal bleeding was the most common symptom in both types of cancer. Spotting and postcoital bleeding occurred more frequently in cervical cancer, but hypermenorrhea was more frequent among the patients having endometrial cancer. Amenorrhea was a complaint in three patients; one had carcinoma of the cervix and was also pregnant.

TABLE III. TYPES OF BLEEDING

	CERVIX	CORPUS
Spotting	25	18
Hypermenorrhea	6	12
Postcoital	5	2
Amenorrhea	2	1
Normal menses	6	2
Postmenopausal	61	61

There was a much higher percentage of women with cervical cancer than with cancer of the corpus who sought medical advice early (Table IV). In the cervical series 62.2 per cent of patients and in the corporeal series only 36.3 per cent consulted a physician within three months after the onset of symptoms. This difference is great enough to require an explanation. Perhaps women who have abnormal menses are less likely to consider this condition serious than those who have vaginal bleeding that is not related to the menstrual cycle.

TABLE IV. DURATION OF SYMPTOMS BEFORE INSTITUTION OF TREATMENT

PERIOD	CERVIX		CORPUS	
	NUMBER OF CASES	PERCENTAGE	NUMBER OF CASES	PERCENTAGE
Less than 3 months	61	62.2	33	36.3
3 to 6 months	14	14.3	13	14.3
6 to 12 months	15	15.3	28	30.7
Over one year	8	8.2	17	18.7
Total	98	100	91	100

The League of Nations criteria were used to determine the stage of involvement in this series. Eighty-five per cent of all the cervical cases were either histologically Grade 2 or 3, and 67 per cent were equally divided between Stage 1 and 2 (Table V). The establishment of the correct clinical stage of involvement is often not accurate. Those who have performed the radical type of hysterectomy for cancer of the cervix have found pelvic lymph node involvement in many patients who were classified as Stage 1 or 2 before operation. However, it is almost impossible to determine this fact by physical examination.

TABLE V. DISTRIBUTION OF CERVICAL CASES ACCORDING TO GRADE AND STAGE

GRADE	NUMBER OF CASES	PERCENTAGE	STAGE	NUMBER OF CASES	PERCENTAGE
1	7	7.2	1	33	33.7
2	48	48.9	2	33	33.7
3	36	36.7	3	28	28.6
4	7	7.2	4	4	4.0
Total	98*	100	Total	98	100

*Squamous carcinoma, 97, adenocarcinoma, 1.

Six patients who had cancer of the cervix had had previous supravaginal hysterectomies. This represents about 6 per cent of the total number of cases in this series. The shortest time between the operation and the appearance of the first symptoms suggestive of cancer was nine years, and the longest interval was thirty-three years. Therefore, the malignancy in all six cases undoubtedly developed after the hysterectomy and was not present at the time of operation.

TABLE VI. DISTRIBUTION OF CORPOREAL CASES ACCORDING TO GRADE AND STAGE

GRADE	NUMBER OF CASES	PERCENTAGE	STAGE	NUMBER OF CASES	PERCENTAGE
1	16	18.6	1	59	68.6
2	50	58.2	2	13	15.1
3	16	18.6	3	9	10.5
4	4	4.6	4	5	5.8
Total	86	100	Total	86	100

Adenocarcinoma	86
Sarcoma	4
Chorioadenoma destruens	1
Total	91

Seventy-six per cent of the corporeal cancers were either Grade 1 or 2 histologically, and 68 per cent were in clinical Stage 1 (Table VI). Thus there were twice as many patients in Stage 1 who had endometrial cancer as there were patients with cervical cancer. The cases of sarcoma, all of which occurred in myomas, and the case of chorioadenoma destruens were not graded nor their stages of involvement determined.

Considerable importance has been given to the role of pregnancy, especially full-term delivery with its production of cervical lesions as a possible cause of cancer of the cervix. In this series, 14.3 per cent of the patients with cervical cancer and 40.6 per cent of those with corporeal malignancy had not been pregnant. This finding compares with 16.6 per cent and 38.6 per cent, respectively, which was reported by Corscaden and Gusberg.

The usual plan of treatment for cancer of the cervix at The Brooklyn Hospital is a full course of deep external roentgen-ray therapy to the pelvis and, in many patients, "contact" roentgen-ray therapy is given directly to the cervix. Approximately six weeks after the completion of the roentgen-ray therapy, radium is placed within the cervix. The radium is usually applied in "T" formation so that the upright arm is within the cervical canal and the cross arm against the vaginal surface of the cervix. The dosages of both the roentgen rays and the radium are individualized. They vary, depending upon the tolerance of the patient, type of lesion, age, etc.

The physical factors of the roentgen-ray therapy were: 200 kv., 20 Ma., 50 cm. distance, and 0.5 mm. on 2 mm. copper filtration with 2 mm. of aluminum. The first patients in this series received radiation therapy through six portals—two anteriorly, two posteriorly, and two laterally. However, at the present time, the two lateral portals are no longer used. The size of the ports varies between 10 by 15 cm. and 15 by 20 cm. The daily amount of roentgen rays given has been between 200 and 300 r. to each of two portals, alternating between the anterior and posterior portals every other day. Lately it has been customary to give the smaller dose of 200 r. to each of two portals daily until a total of 2,400 to 3,600 r. have been given to each portal, depending upon the skin reaction. The smaller daily dose has produced fewer untoward reactions, therefore it has been possible to give a larger total amount.

In those patients having the exophytic type of carcinoma of the cervix with bulky tumors or extensive ulceration and copious bleeding, intravaginal roentgen-ray therapy has been employed in addition to the external radiation. A Phillips contact tube has been inserted into the vagina and placed against the cervix. With 45 kv., 2 Ma., and no filtration, about 4,000 r. have been given. This treatment has been repeated about every ten days until approximately 16,000 r. have been given. Larger amounts have been employed with some patients. This phase of the treatment has been used principally for its local effect of rapidly reducing the size of the mass and curtailing the bleeding.

The use of larger kilovoltages for transvaginal therapy was attempted, but there has been only one patient in this series in whom it could be used satisfactorily. This patient received 135 kv. at 25 Ma. and 0.25 mm. copper filtration.

The radium employed in this series consisted of two platinum capsules 1 mm. thick containing 50 mg. each, and covered by gutta percha 2 mm. thick.

Biopsy specimens have been taken during the course of roentgen therapy in some patients to determine the reaction of the lesion. It has been interesting to note the rapid favorable response of some lesions that cytologically were thought to be radioresistant, and the failure of cytologically immature lesions to respond as rapidly as was expected. We have concluded that there are many undeterminable factors in addition to the cell type that influence the response of cancer to radiation.

There were other methods of treatment used in this series (Table VII). Radium alone was used in connection with eleven patients, but most of them were treated before our institution was equipped to give deep roentgen-ray therapy. The latter treatment without subsequent use of radium was also employed in eleven patients, some of whom failed to return for the application of

radium. Most of the individuals in this group had an advanced process and received roentgen-ray therapy as palliation. The five untreated patients were in the last stages of the disease and were admitted for terminal care.

In order to have a full five-year period for ascertaining the survival rates, none of the patients treated after 1943 were included. There were 69 cases in the cervical group and 62 cases in the corporeal group treated between the years 1935 to 1943, inclusive (Tables VII and X). There was a 40.8 percentage of five-year survivals of the traced patients in the cervical group; this figure included all grades and stages. However, when the cases were analyzed according to grades and stages and their respective survival rates determined, some interesting figures were obtained (Table VIII).

TABLE VII. FIVE-YEAR SURVIVAL OF TRACED CASES OF CARCINOMA OF THE CERVIX, 1935-1943

TYPES OF TREATMENT	NUMBER OF CASES TREATED	CASES TRACED		FIVE-YEAR SURVIVALS									
		NUMBER	DEATHS	NUMBER	PERCENTAGE	GRADE				STAGE			
						1	2	3	4	1	2	3	4
Radium only	11	8	6	2	25	2				2			
X-ray only	11	5	5										
Hysterectomy and x-ray	2	2	1	1	50			1			1		
Radium and x-ray	40	28	13	15	53.5	1	8	4	2	4	7	4	
Untreated	5												
Total	69	43	25	18	40.8	3	8	5	2	6	8	4	0

TABLE VIII. FIVE-YEAR SURVIVAL PERCENTAGES OF TRACED CASES

	GRADE				STAGE			
	1	2	3	4	1	2	3	4
	(PERCENTAGE)				(PERCENTAGE)			
Cervix	66.6	38.9	35.7	66.6	66.6	53.3	26.6	none
Corpus	100	71.4	20	none	82.3	57.1	none	none

Very little, if any, significance could be attached to the relationship between the grade of the tumor and the survival rate. The high percentage of survivals in Grade 4 was of no importance in this series since there were only three cases treated. There was, however, a direct relationship between the extent of the disease at the onset of therapy and the survival rate. The results reported from other institutions are given for comparison with our series (Table IX). They all show the great importance of the relationship between the stage of involvement and the survival rate.

TABLE IX. CARCINOMA OF CERVIX FIVE-YEAR SURVIVAL PERCENTAGES ACCORDING TO STAGES

AUTHOR	STAGES			
	1	2	3	4
Bowing and Fricke	58.8	65.3	33.7	16.5
Buschke and Cantril	83	56	38	
Turtola	62	39.4	19.6	3.6
Maliphant	71.6	33.3	13.7	4.5
Fricke	69.2	60.2	29.7	6.5
Given	58	58		
Hall (this series)	66.6	53.3	26.6	

There have been very few serious complications that could be attributed to the use of radiation. Two patients developed vesicovaginal fistulas after radiation, but extension of the cancer, although never proved, may have been an important factor. One patient had spontaneous femoral fracture apparently resulting from sclerosing osteitis.

The methods of employing radium for the treatment of cancer of the cervix are many and will not be discussed. The implantation of radon needles into the parametrium has found favor with some clinicians, but the reactions of the authors are similar to those of Taylor and Twombly, who conclude that it is a dangerous procedure, at least in their hands.

The treatment of cancer of the endometrium in this series was primarily by the use of intrauterine radium in the form of two 50 mg. capsules in tandem formation, followed in six weeks by a complete abdominal hysterectomy and bilateral salpingo-oophorectomy. A curettage is done at the time of the radium implantation, and a report of the microscopic findings is obtained within four hours. If malignancy is present, 3,600 mg. hr. of radium are given.

Two other methods of treatment for corporeal cancer were used in a considerable number of cases, i.e., radiation only, and hysterectomy only. Radiation without surgery was used when patients were not considered good operative risks. The results obtained from this form of therapy were disappointing (Table X). There was a five-year survival rate of 70 per cent from all forms of therapy, but the best results were obtained by the use of radium followed by hysterectomy. This finding has been noted in numerous reports (Table XI). Over 80 per cent of the patients classed in Stage I survived more than five years, but there were no survivals in Stages 3 and 4. The grade of the tumor in endometrial carcinoma had a much closer relationship to the survival rate than was found in cancer of the cervix (Table VIII).

TABLE X. FIVE-YEAR SURVIVAL OF TRACED CASES OF CARCINOMA OF THE CORPUS, 1935 TO 1943

TYPES OF TREATMENT	NUMBER OF CASES TREATED	CASES TRACED											
		NUMBER	DEATHS	FIVE-YEAR SURVIVALS									
				NUMBER	PERCENTAGE	GRADE				STAGE			
						1	2	3	4	1	2	3	4
Radium only	15	8	5	3	37.5	3				3			
Hysterectomy only	10	9	2	7	77.7	3	3	1		5	2		
Radium and hysterectomy	27	17	1	16	94.1	3	12	1		12	4		
X-ray and hysterectomy	3	3	1	2	66.6		1	1			2		
X-ray and radium	7	3	3										
Untreated													
Total	62	40	12	28	70	9	16	3		20	8		

TABLE XI. CARCINOMA OF CORPUS TREATED WITH RADIUM FOLLOWED BY HYSTERECTOMY

AUTHOR	FIVE-YEAR SURVIVAL PERCENTAGES
Healy and Brown	75
Heyman	78
Ward and Sackett	57.1
Newell and Crossen	63.2
Brindley	79.1
Corscaden	72
Hall	94.1
(this series)	

Adapted from Corscaden: J. A. M. A. 126: 1134, 1944.

The survival rates are high in all forms of treatment of cancer of the corpus provided hysterectomy is part of the therapy. It has already been stated that several patients were not submitted to hysterectomy because they were considered poor operative risks. However, it is possible to operate on many patients nowadays, with the aid of chemotherapy, antibiotics, and blood transfusions, who would have been considered inoperable in the past. We believe, therefore, that a hysterectomy should be performed on all patients who have endometrial cancer unless the odds are overwhelmingly against the successful completion of the operation.

In the cervical series, 72.7 per cent of the deaths and in the corporeal cases, 88.8 per cent, occurred less than three years from the time the diagnosis was established. The prognosis, therefore, for patients having uterine cancer may be considered good if they are alive three years after adequate treatment.

Three of the patients who had sarcoma are alive and well after five years, but one died of sarcomatosis of the peritoneum. The patient with chorioadenoma destruens is also apparently free of any malignancy. It is possible that this last patient should not be classified as having malignant disease since there is some difference of opinion whether this lesion is malignant.

Comment

In this analysis, the survival rates have been computed on the traced cases. This is the same method used at many large clinics such as the Mayo Clinic. However, some workers believe that this method is not accurate. We acknowledge that there may be errors, but we believe that it is erroneous to include all untraced patients among those who died from the malignancy.

Six per cent of the cancers of the cervix occurred in cervical stumps and indicate the desirability of performing a complete in preference to an incomplete procedure in all hysterectomies unless there are strong contraindications.

It would appear that the nulliparous woman is more prone to develop carcinoma of the corpus than the parous woman, whereas the reverse is true in cervical cancer. This fact suggests the possible role that hormonal balance may play in the causation of this disease.

The surgical treatment of cancer of the cervix as advocated by some investigators was not employed in this series. It is possible that the survival rates in the groups in Stage 1 and 2 could have been improved if radical surgical extirpation had been done. However, we have felt justified in not operating on these patients until time has proved the value of the procedure.

The senior author believes that the dosage of radium given after a complete cycle of deep pelvic roentgen-ray treatment for carcinoma of the cervix was too small in many patients. Frequently, as little as 1,200 mg. hr. of radium were used because of fear that the adjacent viscera might be damaged. Would the survival rate have been higher if one had not been so conservative?

It should not be concluded that we believe "contact" roentgen-ray therapy will increase the survival rate. There were nine of the eighteen patients who lived for at least five years after treatment who did not have any form of intravaginal roentgen-ray therapy. However, those patients who had large cervices associated with bleeding and infection had these factors brought under control more quickly when this method of treatment was employed. Also, by controlling the local infection rapidly, the development of parametrial inflammatory processes was diminished.

Whether radium or roentgen rays should be used before hysterectomy when treating endometrial cancer is a debatable point. Miller and Henderson report a higher survival rate when roentgen rays were the form of preoperative radia-

tion. Time may prove that both radium and roentgen rays should be used. The former for its direct effect upon the local lesion, and the latter for its influence on cancer cells in more distant structures such as the parametrium.

At present, a favorable result in the treatment of cancer depends upon treating the lesion in its early phases. The patient must present herself at the first sign of any abnormal symptoms which, in cancer of the uterus, is usually abnormal vaginal bleeding. We must educate the public to realize that not only the cause of vaginal bleeding unrelated to the menstrual cycle should be investigated, but that any change in the menses, especially hypermenorrhea, may be evidence of malignancy. Every woman over forty years of age should have semiannual physical examinations as a prophylactic procedure.

Summary

1. An analysis covering 189 cases of primary malignancy of the uterus has been presented. Ninety-eight cases involved the cervix and ninety-one, the corpus.

2. Sixty-nine patients with cancer of the cervix and sixty-two with cancer of the endometrium were used to determine the survival rates.

3. The five-year survival rate for cancer of the cervix was 40.8 per cent and for cancer of the corpus, 70 per cent.

4. Patients with cervical cancer sought medical advice sooner than those who had corporeal cancer.

5. The histologic grade of the cancer had very little influence on the survival rates in cancer of the cervix, but the stage of involvement was all important.

6. "Contact" roentgen-ray therapy has been an important adjunct in the treatment of cervical cancer.

7. The most important phase in the treatment of endometrial cancer was hysterectomy, but higher survival rates were obtained when radiation was combined with hysterectomy.

References

Bowing, Harry H., and Fricke, Robert E.: J.A.M.A. **137**: 935, 1948.
Brindley, G. V.: Ann. Surg. **114**: 90, 1941.
Buschke, F., and Cantril, S. T.: West. J. Surg. **55**: 152, 1947.
Corscaden, James A.: J.A.M.A. **126**: 1134, 1944.
Corscaden, James A., and Gusberg, S. B.: Am. J. Obst. & Gynec. **53**: 419, 1947.
Fricke, Robert E.: Surg. Clin. North America **27**: 775, 1947.
Given, William P.: Am. J. Obst. & Gynec. **53**: 947, 1947.
Healy, William P., and Brown, Robert L.: Am. J. Obst. & Gynec. **38**: 1, 1939.
Heyman, J., Reuterwall, O., and Benner, S.: Acta radiol. **22**: 11, 1941.
Maliphant, R. G.: J. Obst. & Gynaec. Brit. Emp. **54**: 155, 1947.
Masson, James C., and Judd, David B.: J. Mt. Sinai Hosp. **14**: 483, 1947.
Miller, Norman F., and Henderson, Charles W.: Am. J. Obst. & Gynec. **52**: 894, 1946.
Newell, Quitman U., and Crossen, Harry S.: Am. J. Obst. & Gynec. **29**: 326, 1935.
Taylor, Howard C., Jr., and Becker, Walter F.: Surg., Gynec. & Obst. **84**: 129, 1947.
Taylor, Howard C., Jr., and Twombly, Gray H.: Am. J. Roentgenol. **56**: 513, 1946.
Turtola, Viljo.: Acta obst. et gynec. Scandinav. (supp. 4) **27**: 1, 1947.
Ward, George G., and Sackett, Nelson B.: J.A.M.A. **110**: 323, 1938.

AN UNUSUAL EPIDEMIC OF NEONATAL MASTITIS*

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NURSERY epidemics of neonatal impetigo due to the *Staphylococcus aureus* are not uncommon, but the immature mammary glands are rarely involved, even when there is extensive skin involvement. Consequently, it seems wise to report an outbreak of staphylococcic infections marked by mastitis which resulted in breast abscesses in more than one-half the babies affected. Impetigo was rarely observed. The recent literature contains four reports of mastitis of the newborn, by Corciovei,[1] Garrahan,[2] Pyle,[3] and Winder.[4]

Material

The obstetric and gynecologic service of the Oak Ridge hospital was opened December, 1943. The entire obstetric department was in a single wing of the hospital, with separate delivery and labor rooms. Patients were housed in single and double rooms, and in four-bed wards. Deliveries averaged 100 each month. There were three nurseries, one for full-term infants, another for prematures, and an isolation nursery. The full-term and premature nurseries were staffed by graduate nurses.

The nursery for well, full-term infants was air-conditioned and equipped with sterilamps. The skin care of the newborn consisted of an oil bath and a 2 per cent ammoniated mercury rub given soon after birth, and a subsequent daily oil bath, with a mercury rub on the second and fifth days. The daily care was carried out on a common bath table where all babies were weighed. Soon after the obstetric unit was opened overcrowding became the rule.

The first infant breast infections occurred during September, 1944, and the last in July, 1945. During this ten-month period, twenty-eight infants developed staphylococcic infections. There were eighteen cases of simple or suppurative mastitis. In addition there were eight skin infections of the lower jaw, two paronychias, and two groin abscesses. Two babies each had two sites of infection.

Ninety per cent of the lesions occurred during September, January, June, and July. There were no infections during October, November, April, and May. When the epidemic started, eight cases of mastitis appeared within seven days. The next breast infections did not occur until January, 1945, when there were two cases. The remainder of the cases developed in June and July, 1945.

Little significant information was obtained from reviewing the maternal histories. Fifty per cent of the mothers were primigravidas; most delivered spontaneously, with no pregnancy or labor complications. The incidence of puerperal morbidity (two or more days of fever) was 10.0 per cent which is higher than the average of 7.0 per cent for all patients. There were four maternal breast infections in the twenty-eight mothers. Two developed during the hospital stay and the others one month later. The number of maternal breast infections was appreciably increased during the period under review.

*From the Oak Ridge Hospital, Oak Ridge, Tenn., where the senior author had charge of the Obstetric and Gynecologic Service from December, 1943, to September, 1946.

A brief summary of the data is presented in Table I. Twelve of the eighteen infants (all full-term and normal) who developed mastitis were girls. This sex difference is probably not significant. Thirteen of the infections began between the eighth and tenth days of life. The earliest involvement was the fifth day, the latest on the sixteenth day following birth. The case reports of Corciovei[1] and Garrahan[2] emphasize that the onset of the infection is between the seventh and ninth days.

The usual course of the disease was as follows: The breast first showed marked erythema with considerable induration. If not treated promptly the infection spread rapidly. The appearance was different from ordinary impetigo in that there were no pustules or clear vesicles; the lesions were deeper and had the appearance and course of furuncles rather than of impetigo.

In several instances, where the treatment was stopped too soon, the infants were readmitted several days later with reactivation of the infection. Despite therapy, ten of the eighteen cases developed suppuration, nine were incised and drained, and one drained spontaneously. The amount of pus obtained was small. The infection subsided promptly with adequate drainage. In one case with inadequate drainage, subsequent incision was required. The majority of the cases of mastitis that subsided without abscess formation were treated early and with adequate amounts of the antibiotics. Those with abscess formation were inadequately treated or were first seen after an abscess had formed. The hospital stay of the newborns was prolonged two to four days over the average stay of ten days, with two babies remaining twenty-two days.

When the first infections appeared, the obstetric staff was naturally alarmed because of the number and the unusual locations of the lesions. The infected babies were isolated and were treated by the pediatric and surgical staffs. A new nursery was established and all newborns were housed there until they were discharged. The contaminated nursery was thoroughly cleaned, lysolized, and aired for several days, before being reopened for newborns. This measure seemed effective in that only sporadic cases appeared until June and July, 1945. With this new outbreak, a more thorough investigation was launched.

Nose and throat cultures obtained from the nurses and nurses' aids working in the nursery were positive for *Staphylococcus aureus* in a high per cent. The oil used to bathe the babies was very heavily contaminated with the same organism. Cultures of the nursery air revealed *Staphylococcus aureus*. Checking of the air conditioning units revealed that the filters had not been changed as frequently as required, and that one intake vent had been improperly attached and was drawing air from the hall floor.

The nursery was again cleaned, the nursery personnel changed, oil baths were discontinued, individual bassinet care was instituted, and the defects in the air conditioning unit were corrected. The newborns were given daily water baths and an ointment containing penicillin in a water-soluble base was rubbed daily into the creases of the neck, axillae, and groins. There were no further skin infections.

Discussion

Hart[5] has noted that epidemics of impetigo were reported as early as 1773. As a rule the infection is spread by carriers or from other cases, but sporadic cases may appear from unrecognized staphylococcic lesions. Once an epidemic

TABLE I. SUMMARY OF EIGHTEEN CASES OF SIMPLE OR SUPPURATIVE MASTITIS

NAME	SEX	BIRTH WEIGHT	DAY OF ONSET	PROLONGATION OF HOSPITAL STAY	FINDINGS	TREATMENT	WHITE BLOOD CELLS	TEMPERATURE	CULTURES	RESULTS
Baby R 52936	F	7 lb. 2 oz.	12th	7 days	Erythema, indur. right breast	Penicillin	8,550	Normal	*Staph. aureus* (Hemo)	Incision and drainage
Baby C 70916	F	7 lb. 8 oz.	16th	5 days	Erythema, indur. right breast	Sulfadiazine	31,000	101° F. rectal	*Staph. aureus* (Hemo)	Incision and drainage
Baby S 65153	F	7 lb. 11 oz.	8th	9 days	Erythema, indur. left breast	Penicillin	11,550	Normal	None	Spont. drainage Subsided
Baby H 52892	M	8 lb. 15 oz.	13th	4 days	Erythema, cellulitis, right breast	Penicillin	15,300	Normal	None	Subsided
Baby H 52732	M	9 lb. 6 oz.	14th	12 days 2 admissions	Erythema, indur. right breast	Penicillin	Not done	Normal	*Staph. aureus* (Hemo)	Incision and drainage
Baby R 52463	F	6 lb. 14 oz.	10th	2 days	Erythema, left breast	Sulfadiazine Penicillin	11,800	102° F. rectal	*Staph. aureus* (Hemo)	Incision and drainage
Baby H 68986	M	7 lb. 6 oz.	5th	1 day	Erythema, indur. right breast	Penicillin	Not done	Normal	None	Subsided
Baby D 70355	F	7 lb. 11 oz.	5th	2 days	Erythema, indur. right breast	Penicillin	Not done	Normal	*Staph. aureus* (Hemo)	Incision and drainage

Baby N 52464	F	8 lb.	7th	3 days	Indur. cellulitis, right breast	Sulfa-diazine	12,100	Normal	*Staph. aureus* (Hemo)	Incision and drainage
Baby S 83474	M	10 lb.	9th	2 days	Erythema, indur. left breast	Penicillin	Not done	Normal	None	Subsided
Baby O 66715	F	7 lb. 8 oz.	9th	1 day	Erythema, indur. left breast	Penicillin	Not done	Normal	None	Subsided
Baby W 52321	M	8 lb. 4 oz.	6th	3 days	Marked cellulitis	Penicillin and Sulfadiazine	13,850	102° F. rectal	*Staph. aureus* (Hemo)	Incision and drainage
Baby K 66371	M	8 lb. 11 oz.	9th	13 days 2 admissions	Erythema, indur. right breast	Penicillin	19,100	Normal	*Staph. aureus* (Hemo)	Subsided. Incision and drainage
Baby D 55514	F	6 lb. 13 oz.	10th	9 days 2 admissions	Erythema, indur. right breast	Penicillin	16,900	Normal	*Staph. aureus* (Hemo)	Subsided. Incision and drainage
Baby A 81673	F	7 lb. 4 oz.	6th	1 day	Erythema, left breast	Penicillin	Not done	None	None	Subsided
Baby L 87248	F	6 lb. 4 oz.	9th	1 day	Erythema, indur. left breast	Penicillin	Not done	None	None	Subsided
Baby M 84948	F	7 lb. 5 oz.	12th	1 day	Erythema, right breast	Penicillin	Not done	Normal	None	Subsided
Baby S 84273	F	6 lb. 9 oz.	8th	1 day	Erythema, indur. right breast	Sulfa-diazine	Not done	Normal	None	Subsided

has started, new cases usually result from infection carried from baby to baby on the hands of nurses or doctors, from contaminated laundry, or from actual contact.

Epidemiologic investigations of recent outbreaks of impetigo indicate that staphylococcic infection of the nose and throat in the nurses and attending staff are most often the source of the infection.

The source of the responsible staphylococci is problematic, since the organisms were so widely disseminated before complete bacteriologic studies were made, but it seemed reasonable to incriminate the baby oil which was rubbed into the skin daily. The oil was kept in a large container from which it was poured directly onto the nurses' hands. The container was on the common bath table which was also used for the general care of the children. The freshly oiled skin obviously offered an ideal site for the adherence of dust and bacteria from the contaminated nursery air, thus increasing the likelihood of infection. The presence of staphylococci in the nasal discharge of some of the nursing attendants was probably secondary. The fact that most of the mastitis appeared between the eighth and tenth days of life suggests that the organisms may have entered the mammary ductile system a few days after birth when the withdrawal of estrogen stimulation tends to produce dilation of the orifices of the ducts. Winder[4] has reported a baby with mastitis and widespread impetigo following skin inunctions with contaminated goose grease.

There was no evidence that any nurse, nurses' aid, or mother was massaging the child's breasts or attempting to express the "witches milk." Most authors have reported that massage or squeezing of the engorged breast is provocative of infection. The possibility that this particular strain of staphylococcus had a predilection for breast tissue was not explored.

In twelve instances the mastitis involved female infants of whom seven developed abscesses requiring drainage. One wonders what effect this will have on future breast development since in some instances there was considerable destruction of breast tissue. Kalbow[6] reported an interesting patient whom he followed for many years after draining a left-breast abscess in the neonatal period. After puberty, the left breast was much smaller with only a small portion of glandular tissue in an upper quadrant, the rest being scar tissue. The girl eventually married and became pregnant. Lactation in the involved breast was inadequate and within thirty days the child was being fed entirely from the right breast. Other German authors do not consider the effect on subsequent breast development and function as serious as does Kalbow. It is hoped that some of these babies may be followed so that more information on this matter may be obtained.

Conclusion

This epidemic of neonatal mastitis is reported because of (1) the large number of children involved; (2) the high percentage of cases requiring incision and drainage; (3) the probability that the bath oil was the source of infecting organisms; and (4) the possible destruction of enough breast tissue to

prejudice pubertal breast development in female children treated by incision and drainage.

References

1. Corciovei, I.: România med., Bucharest **13**: 283, 1935.
2. Garrahan, J. P.: Rev. de especialid., Buenos Aires **1**: 526, 1926.
3. Pyle, Lucien R.: Am. J. Obst. & Gynec. **55**: 676, 1948.
4. Winder, F. A.: Med. Press & Circ., London **68**: 632, 1899.
5. Hart, J. Dudley: Brit. M. J. **1**: 623, 1943.
6. Kalbow, Heinrich von: Zentralbl. f. Gynäk. **60**: 1821, 1936.

Albert, Alexander: Evaluation of the Hyperemia Test for Pregnancy as a Routine Clinical Laboratory Procedure: Comparison of Results With Those of 1,000 Consecutive Friedman Tests, Proc. Staff Meet., Mayo Clin. **24**: 259, 1949.

A comparison of the ovarian hyperemia test in rats with the Friedman test as a procedure for diagnosis of pregnancy was made in 1,000 cases. In 30 cases the Friedman test could not be completed because of toxicity of the specimens to the rabbits. In the 970 cases in which both tests were completed, the results were in agreement in 924 cases, not in agreement in 46 cases. In 475 of the 924 cases, both tests gave positive results, and in 449 cases, negative results. In the 30 cases in which only the rat test was done, 18 tests were positive and 12 were negative. In the 18 cases in which the test was positive, there were 12 apparently normal pregnancies, 2 cases of chorion epithelioma, 2 cases of spontaneous abortion. One patient could not be followed up. In the 12 cases in which the rat test was negative, 8 patients were not pregnant, 2 patients were aborting when the test was made, one had had a hydatid mole removed, and one could not be followed up. In the 46 cases in which the rat test and the Friedman test were not in agreement, there were 16 cases of abortion or threatened abortion in which the Friedman test was positive and the rat test negative. In 9 cases in which the pregnancy was excluded, the rat test gave a correct negative result, the Friedman test was positive. In 8 cases of pregnancy, the Friedman test was negative and the rat test correctly positive. However, in 7 cases of very early pregnancy, the Friedman test gave positive results; the rat tests negative results; in one case of hydatiform after operation, the Friedman test was positive and the rat test negative. In 5 cases in which the tests did not agree, no clinical diagnosis is available.

A study of the sensitivity of rabbits (used in the Friedman test) to chorionic gonadotropin as compared with that of rats shows that the rabbit test will be positive when the concentration of gonadotropin in the twenty-four hour urine specimen is 500 I.U. or more; but that the rat test will be positive when the concentration reaches 1,000 I.U. or more. If the tests are made in very early pregnancy, when the level of chorionic gonadotropin is between 500 and 1,000 I.U., the Friedman test will be positive and the rat test negative (as noted above in 7 cases of very early pregnancy). Following abortion or fetal death, when the level of excretion of the hormone is falling, the rat test will become negative before the Friedman test. In cases of abortion or threatened abortion, the negative rat test may be of more clinical importance, as predicting that abortion is inevitable.

On the basis of these findings, the authors conclude that the rat test is as accurate as other tests for pregnancy, and probably more accurate than the Friedman test. The disadvantage of the lesser sensitivity of the rat test in very early pregnancy can be offset by repeating the test in a few days or by injection of twice the amount of urine. The rat test is simpler to perform and gives results in four hours, and is much more convenient to use in the laboratory, because of the availability of a uniform strain of test animals.

Harvey B. Matthews.

THE MALE FROG (RANA PIPIENS) AS A TEST ANIMAL FOR DETERMINING THE LEVEL OF URINARY CHORIONIC GONADOTROPHIN DURING PREGNANCY

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GALLI MAININI first described sperm release from the testes of the South American toad, *Bufo arenarum*, by chorionic gonadotrophin (CU). Shortly thereafter Wiltberger and Miller[2] and Robbins and Parker[3] showed that the same phenomenon occurred in the North American frog, *Rana pipiens*. Thus this abundant and cheap animal was available for pregnancy tests. The procedure is a simple one and positive results can be obtained in one to three hours. Unquestionably it is one of the most rapid, least complicated, and most inexpensive pregnancy tests yet devised. Whether these qualities are matched by reliability and accuracy remains to be seen.

In this study urines from 108 proved pregnancies in all stages of gestation were tested. Serial dilutions of the pregnancy urines were made to determine roughly the level of gonadotrophin excretion and the sensitivity of the test. In addition, even though others had done this before, we also ran parallel determinations on the frog and the rabbit in order to compare the results of the frog test and the Friedman test.

Material

Urines were obtained from patients in all stages of gestation, whose histories were available to us. In addition we included urines from a few private patients whose histories were not available to us, but whose urines were sent to the University Hospital laboratories for testing. We were able also to include a small group of menopausal urines obtained from the outpatient department of the University Dispensary.

The frogs used *(Rana pipiens)* were all large adult males obtained from a dealer. The frogs were kept indoors in large concrete tanks through which ran a stream of cold water. Otherwise the animals were handled as recommended by Miller and Wiltberger.[4] All tests were made during the months of November to February, inclusive.

Method

Voided pregnancy urines were obtained at any time day or night and stored as a rule in the refrigerator until tested. Refrigeration, however, was not strictly necessary as we were able to obtain positive results with urines kept at room temperature for over a week. Four frogs were injected with 4 c.c., 2 c.c., 1 c.c., and 0.5 c.c., respectively, the three smallest amounts being brought to 4 c.c. volume with distilled water. The urine was injected under the skin on the back surface (dorsal lymph sac) with a hypodermic syringe

and a 22 gauge needle. The frogs were then placed at room temperature in a dry 1 L. beaker, suitably covered to prevent escape. At the end of one hour a drop of urine from the bottom of the beaker was placed upon the slide and examined microscopically under low power. If the frog had not urinated voluntarily, it would usually do so when grasped by the neck. With practice it was possible so to hold the frog that it would usually urinate directly on the slide. In some stubborn cases urine could be produced only after pressure on the bladder or alternate extension and flexion of the legs. In positive tests the characteristic cigar-shaped motile sperm are easily recognized and are almost always present an hour after the injection. However, with some of the weaker dilutions sperm were sometimes not seen for two hours. If no sperm were seen after two hours, the test was considered negative.

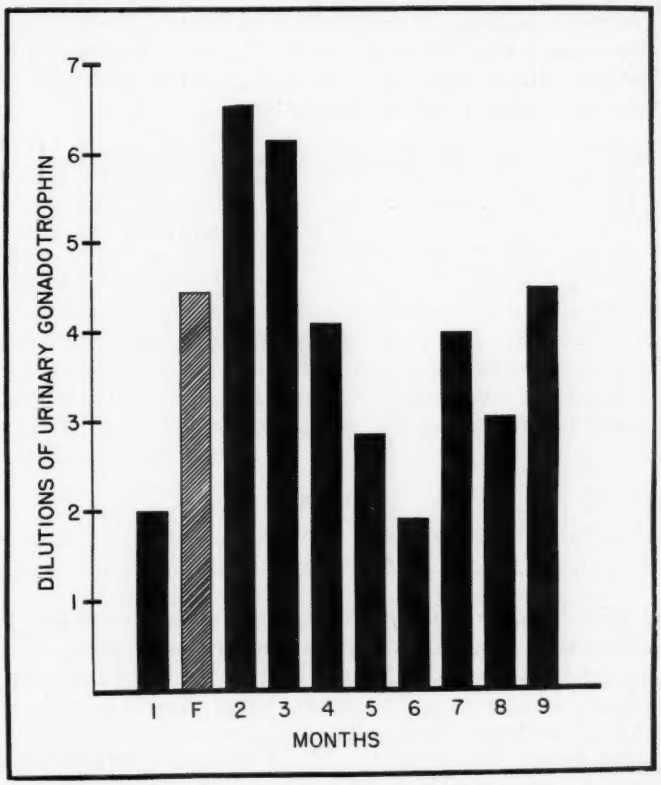

Fig. 1.—Average amount of chorionic gonadotrophin (CU) during each month of pregnancy as determined by the frog sperm release test using serially diluted urines. F = urines collected for Friedman tests from subjects presumed to be between one and two months pregnant.

Frogs which gave a negative response could be reinjected at any time. Those which gave a positive response were segregated and not used again for at least five days, and usually not for one week. In these experiments over 155 specimens of urine were tested, each urine usually being administered in four different dilutions to four different animals. For these tests 140 frogs served.

In our early tests many of the animals died, apparently due to toxic properties of the sediment. To avoid this loss, before injection we routinely centrifuged or filtered all urines which contained any appreciable amount of

sediment. With this procedure undesirable reactions were reduced to a minimum. In no case did we attempt to adjust pH or otherwise alter the character of the urine.

Results

Table I summarizes the data obtained with 108 proved pregnancy urines, with 5 menopausal urines, and with 17 urines which gave positive Friedman responses in rabbits. Of the pregnancy urines, 87 gave positive responses, or 80.5 per cent of the total. However, inspection of the table shows that all the negative responses were obtained with urines collected during the fourth or eighth month of gestation. No negative responses were obtained with urines collected during the first trimester, nor were there any negative responses with nine-month urines. In the latter instance, however, there is considerable doubt as to the significance of the result because of the small number of cases. The highest frequency of negative responses occurred during the sixth month. No positive responses were obtained with the five menopausal urines. The urines which gave positive responses on rabbits were assumed to be from patients in the first or second month of pregnancy.

TABLE I. RESPONSES OF PREGNANCY AND MENOPAUSAL URINES IN VARIOUS DILUTIONS WHEN TESTED FOR PRESENCE OF CHORIONIC GONADOTROPHIN (CU) ON MALE FROGS

URINE	DILUTIONS GIVING POSITIVE TEST				NEGATIVE IN ALL DILUTIONS	TOTAL	PER CENT POSITIVE TESTS
	1-0	1-1	1-4	1-8			
Positive Friedman	2	5	4	6	–	17	–
Menopausal	0	0	0	0	5	5	0
Pregnancy month							
1	2	0	1	0	0	3	100
2	1	1	0	7	0	9	100
3	1	2	5	13	0	21	100
4	4	5	0	10	4	23	83
5	0	7	2	3	4	16	75
6	1	0	1	2	7	11	36
7	0	2	0	3	2	7	71
8	3	2	1	4	4	14	71
9	0	1	2	1	0	4	100

In Table II all of the urines which were tested on frogs and rabbits are included. In these cases the following procedure was adopted. Part of the sample was injected into the rabbit and the remainder was made available for testing on the frog. As before, the frogs were injected with four dilutions. The results of the Friedman tests were not known until after the results of the frog tests had been determined. The Friedman tests were made by the regular staff of the Universtiy Hospital Laboratory.

TABLE II. COMPARATIVE RESULTS IN TESTING FOR CU ON RABBIT (FRIEDMAN TEST) AND FROG

	NUMBER	POSITIVE FROG	NEGATIVE FROG	PER CENT AGREEMENT IN FROG
Positive rabbit	23	19	4	82.5
Negative rabbit	10	1	9	90.0

In all, thirty-three specimens were injected into rabbits and frogs. The results are shown in Table II. Comparisons of this sort are not conclusive since false positives may occur in Friedman tests when female rabbits come into close proximity with other does, or with bucks. False negatives can also be obtained in rabbits. It is impossible to tell why the urines which gave positive tests on the frog failed to produce positive results on the rabbit. We know of no conditions under which false positives are likely to occur in the

frog, but we cannot be sure since there may be circumstances under which they occur, about which we are ignorant. However, we have obtained positive responses in the frog with first-trimester urine in amounts as small as 0.1 c.c. and it is our impression that the frog test is more sensitive than the rabbit test for early pregnancies.

Two urine samples were tested within two weeks after the first missed period and were recorded as "weakly positive." Only a few sperm were found in the drops examined. A week later both patients gave strong positive responses. We therefore believe that a positive response cannot be obtained with certainty before the fourth week of pregnancy and that no negative test at this stage should be accepted unless another negative response is obtained a week later. Robbins and Parker[3] reported a positive response seven days after the first missed period.

In an attempt to determine in a semiquantitative way the level of gonadotrophic excretion during the entire period of pregnancy, the data in Table I were treated as follows. Urines which were positive only when injected in 4 c.c. doses were scored 1, urines positive in 2 c.c. doses were scored 2, urines positive in 1 c.c. doses were scored 4, and urines positive in 0.5 c.c. doses were scored 8. Since a 1 to 8 dilution is by no means the maximum capable of giving a positive response, this method undoubtedly underestimates the potency of those urines containing a high level of gonadotrophic activity. However, it serves adequately to reveal any shifts in gonadotrophic excretion throughout pregnancy. The average score for each month is plotted in Fig. 1. Those urines which gave positive Friedman values are plotted between the first and second months, since the urines were collected at random, presumably from patients in the first and second months of pregnancy. As would be expected, the highest concentration of gonadotrophin in the urine comes at two months and the lowest concentration at six months. From the sixth month on the concentration rises until term, although it never again reaches the high level attained during the second month.

Discussion

Sperm is ordinarily released from the testes of the male frog when it clasps the female during copulation. The activating agent is luteinizing hormone (LH), secreted by the pituitary probably in response to nervous stimulation. Just what the precise central nervous pathways are is not known, but no other type of stimulation, including the excitement generated by handling, is known to release LH. However, LH is not the only hormone capable of initiating this response since it is obvious that chorionic gonadotrophic (CU) will do the same. This is not surprising since the actions of these two hormones closely parallel each other in many respects. Apparently follicle-stimulating hormone does not release sperm, at least not in amounts ordinarily found in menopausal urine.

We found the frog test to have an accuracy of 100 per cent during the first trimester of pregnancy. After the third month, however, its effectiveness drops off rapidly and is at its lowest ebb during the sixth months. It rises again during the last trimester, but never, except possibly in the ninth month, does it reach the level seen during the second month. Our data are in close agreement with what is known regarding the excretion levels of gonadotrophin during pregnancy. Our results also agree in general with those of Miller and Wiltberger,[4] who report that 50 per cent of their tests were negative when run on urines collected after the first trimester. Robbins and Parker[3] report that in a study of seventy-seven known pregnancies they observed no negative responses. They do not state, however, at what stage of gestation their urines were collected. Presumably they were from the first trimester.

Because of the large number of negative responses seen in urines collected during the second and third trimester, we do not consider the frog test reliable at this time. Therefore it is not indicated in procedures for determining death in utero, retained viable chorionic tissue, or conditions of late pregnancy. However, its high degree of accuracy during the first trimester makes it an ideal pregnancy test because of its simplicity and cheapness.

Galli Mainini[1] has made observations on the effect of urines other than those collected during pregnancy. He reports consistent negative results with urines taken from children, nonpregnant females, women past the menopause, and males. He also observed that the injection of estrogens, progesterone, testosterone, thyroxin, insulin, Adrenalin, and desoxycorticosterone into toads failed to release sperm. His toads responded to 100 units or more of chorionic gonadotrophin and 500 units or more of serum gonadotrophin. The test, therefore, seems to have a high degree of specificity for CU and LH.

In comparing results with Friedman tests, Galli Mainini reported that ninety-four out of ninety-nine parallel tests were in agreement. In those that disagreed, the toad was positive and the rabbit negative three times. The toad was negative and the rabbit positive twice. These results are somewhat better than ours. We found twenty-eight out of thirty-three tests in agreement on both frogs and rabbits. Of the remainder one was positive on frogs and negative on rabbits, while four were negative on frogs and positive on rabbits.

Summary

Urines containing adequate amounts of chorionic gonadotrophin (CU) will bring about the release of sperm when injected into male frogs. Using this as a test for the presence of CU, the following results were obtained with various urines.

1. Positive responses were seen in 87 out of 108 urines collected in all stages of gestation.

2. No negative responses were obtained from urines collected during the first trimester.

3. Concentration of CU was highest during the second month and lowest during the sixth month. From the sixth month on it tended to increase gradually, but never reached the level seen during the second month.

4. Parallel tests run on rabbits (Friedman test) and frogs gave agreement in twenty-eight cases out of thirty-three.

5. No positive responses were obtained with menopausal urines.

We wish to express our appreciation to the Departments of Gynecology and Obstetrics for their assistance in securing urines for us. We are also indebted to the Department of Clinical Pathology for aid in helping us to run parallel determinations on rabbits and frogs.

This work is part of the program relating the basic sciences to obstetrics and gynecology, sponsored by the Postgraduate Committee of the University of Maryland School of Medicine.

References

1. Galli Mainini, C.: J. Clin. Endocrinol. 7: 653, 1947.
2. Wiltberger, P. B., and D. F. Miller: Science 107: 198, 1948.
3. Robbins, S. L., and Parker, F., Jr.: Endocrinology 42: 237, 1948.
4. Miller, D. F., and Wiltberger, P. B.: Ohio J. Sci. 48: 89, 1948.

AN EVALUATION OF THE MALE FROG PREGNANCY TEST

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THIS paper presents the results obtained in an investigation of the male frog test for pregnancy compared to the Friedman modification of the Aschheim-Zondek test in a series of 52 urine samples from 47 cases and correlated with the clinical follow-up. This study was stimulated by the report of Galli-Mainini[1] who first reported his results in 1947 using the male Batrachia *Bufo arenarum* Hensel as the testing animal. In 1948 the same author[2] reported an accuracy of 98 to 100 per cent in 2,661 accumulated cases using the same toad. About the same time Wiltberger and Miller[3] reported equally striking results using the male leopard frog *Rana pipiens*, which is indigenous to this country, and the animal used in this study. Since then Robbins and Parker[4] (*Rana pipiens*), Brody[5] (*Rana pipiens*) and Haines[6] (*Bufo arenarum* Hensel) have reported fairly large series of cases with some few failures, an experience encountered more frequently by the present authors.

The male frog test as a biologic test is based on the observations of de Robertis, Burgos and Breyter,[7] who in 1945 and 1946 described the action of gonadotropic hormone on the male frog. The substance produced spermatogenesis in the male frog, an activity which occurs normally only during sexual stimulation. They thus concluded that spermatogenesis in the male frog was under the control of the anterior lobe of the pituitary gland.

Technique

One adult frog, *Rana pipiens*, and in some instances two or three animals, were used for each test, and at the same time a Friedman Aschheim-Zondek test was performed on each urine sample submitted. The frogs were all carefully examined to determine sex, as indicated by the large hooked thumb and the elicitation of the amplexus reflex. In some instances, especially with those frogs which gave false negative tests, histologic confirmation of sex was performed. Furthermore, in some instances where false negative results were obtained with certain frogs, repeat determinations were performed with the same frogs using known positive urines with positive results. This also served to confirm the sex of these animals. The frogs were bought at small cost from biological supply houses. They were easily maintained in metal or glass containers and fed daily on meal worms and kept moist. The animals were reused after a four-day interval.

The test was performed by injecting, subcutaneously, into the dorsal lymph sacs 3 c.c. of untreated morning urine (filtered only if there was some sediment). Three c.c. was selected as an average of that recommended by Wiltberger and Miller.[3] At one, two, and four hours, cloacal fluid specimens were taken from the frog by means of a capillary glass tube, placed on a microslide, and examined microscopically unstained and with reduced light for spermatozoa. The finding of one to many spermatozoa indicated a positive result. The sperm

sluggishly motile, with highly refractile, long, fusiform-shaped heads, were seen by low-power magnification, and if necessary confirmed by high-power visualization.

Results

In all, 52 urine specimens from 47 patients were tested by both the frog and Friedman Aschheim-Zondek techniques. Of these, twenty-three were positive with the Freidman method and only fourteen were frog positive. Clinical follow-up indicated that the Friedman tests were all accurate without exception. Therefore, there were nine false negative frog tests. This leaves an 84 per cent accuracy of the frog test as compared to a 98 per cent accuracy for the Friedman method in this series.

Eighty-seven per cent of the positive frog results were observed in two hours or less. Of these, 50 per cent were positive in one hour or less. The earliest positive frog test was observed at one-half hour, and the latest at four hours. With two exceptions all cases were those of early suspected pregnancies. One of the exceptions, a young man, was suspected of having a testicular tumor, and proved negative. The second, a seven-month gestation with slight vaginal bleeding, gave negative results with both frog and rabbit. There was no instance of a false positive frog test in the cases of early gestation.

Comment

The results of our investigation would indicate that the frog test in our hands is not as accurate as has been reported by others. Nor is the frog test as accurate as the Friedman modification of the Aschheim-Zondek test. Furthermore, it must be pointed out that the search for spermatozoa is often tedious and presents a possible source of error, inasmuch as at times the flora of the frog cloaca can readily be confused with spermatozoa by untrained personnel.

However, in its favor, it may be said that the frog test is rapid, inexpensive, and reliable when positive. In this respect the test may have some value in instances where a rapid diagnosis is desired as in possible ectopic gestation. As an example of the above, one positive frog test was obtained in this series in a case of suspected ectopic gestation while the patient was being prepared for operation. Operation disclosed a tubal abortion. Furthermore, from our material it would seem that the frog test will give a positive result as early as the rabbit. The earliest positive frog and rabbit tests were observed in one case eleven days after a missed menstruation.

We are unable to offer any explanation for the high percentage of failures encountered with the frog test, as it was performed in this study. One experiment can be cited which emphasizes the weakness of the male frog test. Three frogs were used in one test in addition to the rabbit. One of the frogs gave a positive result, and the other two gave a negative result despite the usual diligent search. Later the two latter frogs were reused with another sample of urine to be tested. On this occasion both frogs, previously negative, gave a positive result.

Summary

1. Fifty-two urine samples were tested for pregnancy in 47 cases by using the male leopard frog *Rana pipiens*, as well as the female rabbit as in the Friedman modification of the Aschheim-Zondek test, and were correlated by later clinical follow-up.

2. Ninety-eight per cent accuracy was observed with the Friedman test, and only 84 per cent accuracy with the male frog test.

3. The male frog test, as now performed, may have value when positive where a rapid diagnosis of pregnancy is desired as in ectopic gestation.

References

1. Galli Mainini, C.: Semana méd., Buenos Aires **54**: 337, 1947.
2. Galli Mainini, C.: J.A.M.A. **138**: 121, 1948.
3. Wiltberger, P. B., and Miller, D. F.: Science **107**: 198, 1948.
4. Robbins, S. L., and Parker, F., Jr.: Endocrinology **42**: 237, 1948.
5. Brody, H.: Am. J. Obst. & Gynec. **57**: 581, 1949.
6. Haines, M.: Lancet **2**: 923, 1948.
7. de Robertis, E., Burgos, M. H., and Breyter, E.: (a) Rev. Soc. argent. de biol. **21**: 269, 1945; (b) Proc. Soc. Exper. Biol. & Med. **61**: 20, 1946.

Gellis, Sydney S., White, Priscilla, and Pfeffer, William: Gastric Suction: A Proposed Additional Technic for the Prevention of Asphyxia in Infants Delivered by Cesarean Section. A Preliminary Report, New England J. Med. **240**: 533, 1949.

This report is gathered from The Children's Medical Center and the Faulkner Hospital, and the Department of Pediatrics, Harvard Medical School. It may lead to a reduction of the immediate fetal mortality of those infants delivered by cesarean section.

It has long been observed that the increased respiratory rate, cyanosis, and retraction of the soft parts of the chest were the most constant abnormal findings in the neonatal course of these cesarean babies. Delivery by cesarean section increases the likelihood of aspiration of amniotic fluid, and such aspiration seemed a likely explanation for the obstructive respiratory signs present immediately after birth.

To test this hypothesis two series of infants of diabetic mothers were studied. All mothers received spinal anesthesia without analgesia and were delivered by cesarean section in the thirty-eighth week of pregnancy by the same obstetrician. All infants were observed, and all initial gastric suctions were performed by the same person.

The infants were delivered as quickly as possible to minimize the opportunity for crying or gasping before extraction of the head. The clearing of the airway and administration of oxygen were performed in a uniform manner on the infants.

The infants were placed in incubators with oxygen flowing constantly at the rate of 6 liters per minute. Suction of the nares, nasopharynx, mouth and oropharynx was carried out by the nurse every three hours for the first twelve hours. No attempt to reduce oxygen was made until the fourth day of life. Glucose feedings were started at 36 to 48 hours after birth, and a 2 per cent milk formula at 72 hours.

Four infants in one group of 25 receiving suction developed mild respiratory difficulties as compared with 25 in another group who did not receive suction. Nine of these, though normal at birth, developed marked severe respiratory difficulties, and in six it was present at birth. No deaths occurred in either groups.

The amount of gastric contents in Group I ranged from 10 c.c. to 36 c.c. of five infants delivered by low forceps the gastric contents averaged from 0 to 7 c.c.

As a result of these preliminary studies, the following conclusions seem justified: infants of nondiabetic mothers delivered by low forceps have very small amounts of gastric contents; infants of diabetic and nondiabetic mothers delivered by cesarean section have large amounts of gastric contents immediately after birth; and gastric suction in infants of diabetic mothers appears to decrease the frequency of respiratory difficulties following birth.

It is, therefore, proposed that gastric suction at birth be carried out in infants delivered by cesarean section in addition to the procedures now commonly employed for the prevention of asphyxia.

James P. Marr.

FETAL NANOSOMIA AND BONE ATHREPSIA IN THE NEWBORN OF A WOMAN WITH A SEVERE CYANOTIC CARDIOVASCULAR ANOMALY

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IT IS believed that the adequacy of maternal nutrition during pregnancy is reflected by the physical condition of the fetus and newborn. It is said,[1] for example, that a positive correlation exists between the weight and length of the babe on the one hand, and the quality and quantity of its mother's protein intake on the other.

These observations find their counterpart in experimental work which shows the effects of nutritional deficiency[2] upon fetal and newly born bone. They run the gamut from simple arrest of growth to congenital anomalies. The changes are nonspecific. Descriptions of similar nonspecific bone lesions in man could not be found; however, in the course of routine pathologic examinations of fetuses and newborns an unusual lesion was noted in a term child (No. 5377) and considered an example of nonspecific bone athrepsia.

Materials

Control material utilized in this study consists of long bones (femur, tibia, humerus, ribs) of all premature and term babes autopsied in the Department of Pathology of Duke University Medical School between April 25, 1947, and Feb. 23, 1948: a total of 88 cases, 29.3 per cent of all autopsies performed within this period. Two cases were eliminated, since no bone sections or specimens could be found, reducing the number to 86 (Table I). In many, several bones were present, in others only one, usually the femur. All were decalcified and prepared for microscopic study with hematoxylin-eosin stain. Special stains were limited to an occasional Masson trichrome for connective tissue, Foote's silver for reticulum and Levaditi for spirochetes.

Table I. Eighty-Six Fetuses, Stillborns and Newborns Whose Long Bones Were Examined as Controls for Case No. 5377

AGE IN MONTHS' GESTATION	MALE	FEMALE	SHORTEST CROWN-HEEL LENGTH (CM.)	LONGEST CROWN-HEEL LENGTH (CM.)	LENGTH OF PATIENT WITH LESION (CM.)	CAUSE OF DEATH: FETAL	CAUSE OF DEATH: MATERNAL	CAUSE OF DEATH: UNKNOWN	TOTAL
5-6	3	4	28	36	—	3	2	2	7
6-7	12	17	21	50	36[c] 42[s]	13	14	2	29
7-8	9	6	31	45	31[s]	10	3	2	15
8-9	19	13	35	58	35[s]	9	19	4	32
Unknown	1	2	37	40	—	2	1		3
Total	44	42		—	—	37	39	10	86

c, Chondrodysplasia.
s, Syphilis.

Case History

CASE 5377.—The mother, a 26-year-old pregnant white multipara, one of eight normal siblings, gave a lifelong history of cyanosis due to the presence of cardiovascular anomalies. These were diagnosed at first as tetralogy of Fallot, then as Eisenmenger's syndrome, and last as tricuspid valve atresia, and were accompanied by polycythemia (21.5 Gm. hemoglobin

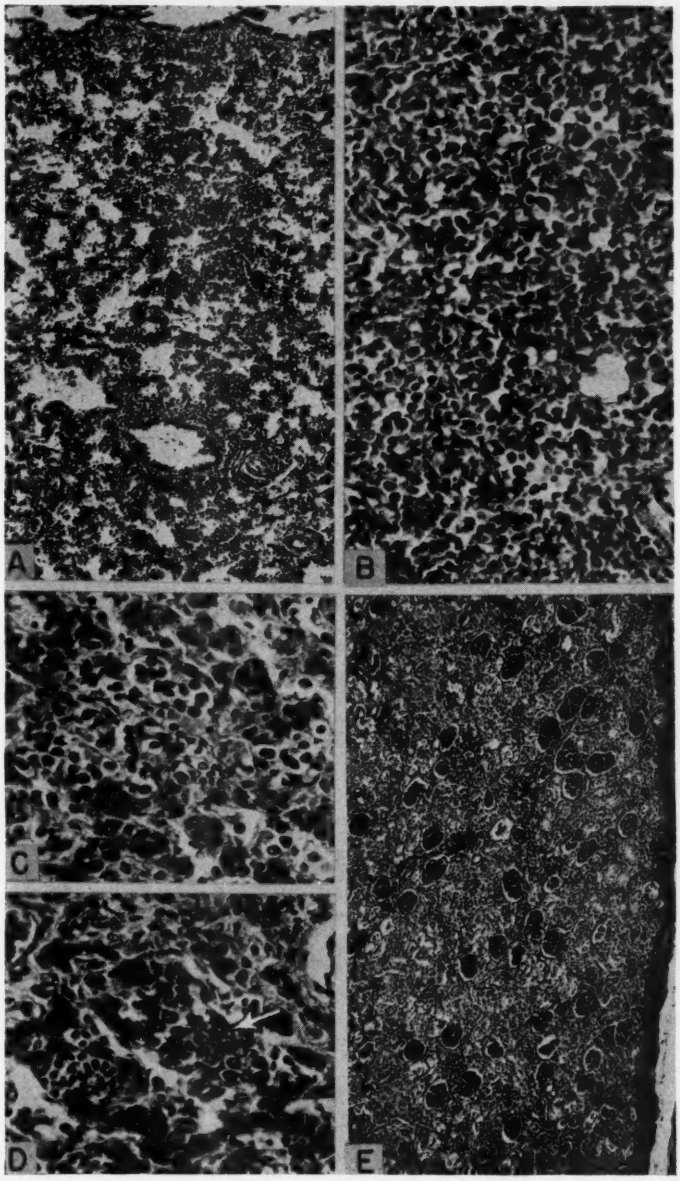

Fig. 1.—A, Marked congestion of lungs. B, Excessive splenic blood production. C, Hepatic blood production. D, Arrow indicates focus of "stem cells" in liver. E, Kidney showing normal term structure of glomeruli.

per 100 c.c. blood) and hypertrophic pulmonary osteoarthropathy. Her child, a male, was delivered at term by low forceps extraction. Although the period of gestation had been nine calendar months, the babe measured but 38 centimeters from crown to heel and weighed 1,400

grams. The placenta weighed 425 grams. Serologic tests for syphilis were negative both in mother and child. The child survived thirteen hours, developing cyanosis several hours before death.

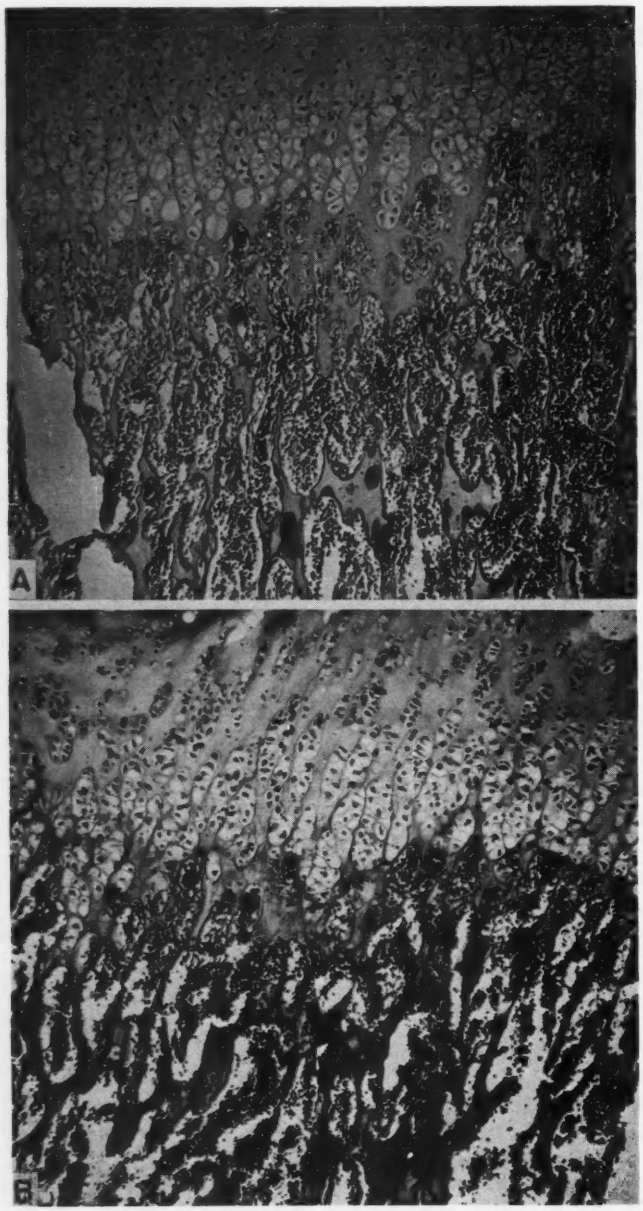

Fig. 2.—A, Costochondral junction revealing widened zone of provisional calcification, irregular bone spicules with thickened transverse trabeculae of calcified cartilage. B, Femur showing irregular line of ossification.

Autopsy.—The heart weighed 14 grams and was not unusual.

All lobes of both lungs were heavy, noncrepitant, and sank in water. They were purple red, markedly congested and atelectatic. Histologic examination revealed (Fig. 1) the alveolar capillaries completely distended and filled with blood which had spilled into some of the alveoli. Pulmonary edema was absent, and amniotic fluid in nonexcessive amounts was present.

The remaining organs revealed no gross abnormalities, but the spleen, liver, bone, and kidneys showed interesting histologic aspects.

The lymphoid follicles of the spleen were characteristic of the term infant, being composed entirely of lymphoid elements. Within sinusoids and parenchyma were superabundant foci of hematopoiesis largely erythrogenic (Fig. 1, *B*).

The liver likewise contained much hematopoiesis, both intra- and extrasinusoidal. This again showed both red and white cell production. The cells, representing various stages in development, were pleomorphic (Fig. 1, *C*). In addition to the above, there were numerous foci of large cells with relatively pale cytoplasm, containing single large nuclei with clearly visible nucleoli (Fig. 1, *D*). These resembled foci of acute myeloblastic leucemia, and were obviously undifferentiated "stem cells" not customarily seen in such numbers in the normal term or premature liver.

The kidneys were completely mature organs, as indicated by the absence of glomerular neogenesis (Fig. 1, *E*), a most important anatomic indication of the child's ripeness.

Rib (Fig. 2, *A*) and femur (Fig. 2, *B*) showed changes which, although similar, were more pronounced in the rib. The columns of hypertrophic cartilage cells were somewhat irregular, and it was apparent that their opening was proceeding at an uneven pace, resulting in an irregular line of ossification. The zone of provisionally calcified cartilage was widened and marked by prominent transverse trabeculae distorting the usual parallel vertical arrangement of the ossifying spicules. These showed a reduction in the amount of osteoid tissue with which they are customarily lined. Corresponding to this change was a persistence diaphysealward of large amounts of cartilage enclosed within bony trabeculae. The marrow was actively hematopoietic and not sclerotic. Unfortunately, only decalcified bone was preserved, preventing investigation of this mineral component.

Discussion

The diminutive stature of the term infant, 38 centimeters crown-heel length and 1,400 grams weight, is most unusual. Stander[3] reported that among 18,160 full-term infants, the lightest weighed 1,660 grams. The mother of our patient, even before pregnancy, was utilizing her circulatory and oxygen transport systems near or at their maximum; she regularly developed dyspnea upon ascending one flight of stairs. As pregnancy progressed, her minimal cardiac reserve disappeared and near term she was confined to bed, her oxygen needs supplemented by tank oxygen. Her hemoglobin coincidentally decreased to 16.4 Gm. per 100 c.c. blood, representing a dilution phenomenon due to both increased blood volume of pregnancy and a degree of anemia of pregnancy. In all probability, the limiting factor to fetal growth was maternal oxygen supply, 1,400 grams representing the maximum fetal size concordant with the hemodynamics of the situation, and the available oxyhemoglobin.

That the oxygen content of the fetal blood differed from that of a normal fetus may be deduced by indirect evidence. The extraordinary amount of blood production, largely erythropoietic, in the spleen, and less so in the liver, may indicate that the fetal blood oxygen content was significantly lower than normal and stimulated the same reaction as is encountered in some adults suffering chronic hypoxemia, namely, excessive extramedullary hemopoiesis. Not one of the control fetuses showed splenic blood production even remotely comparable to that of Case 5377. The hemopoiesis in the liver may be quantitatively matched in term children of normal weight; however, the foci of highly undifferentiated "blast" cells are altogether atypical and are considered to represent accelerated blood production in response to unusually low blood oxygen.

Bone.—Table I reveals that, of the 86 controls, in only four instances were bone lesions recognized. Three showed characteristic syphilis and one chondrodysplasia. In none (Fig. 3) were lesions seen comparable to that

of Case 5377. Special attention was paid the bones of the shortest fetuses and newborns of each age group. Two of the three syphilitics were the smallest in their respective groups: 7-8, 8-9 months' gestation. Case 5377 would have been third smallest in its group, measuring just 3 centimeters longer

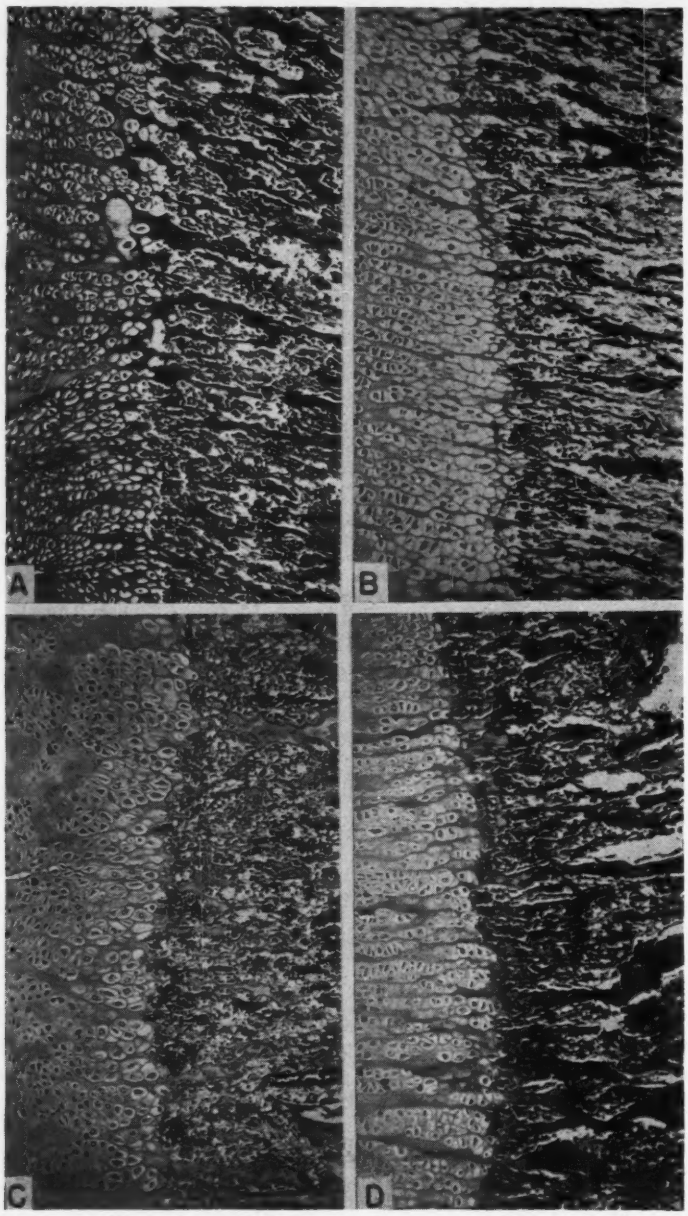

Fig. 3.—Normal bone formation of premature and term newborn infants. A, 5-6 months. B, 6-7 months. C, 7-8 months. D, 8-9 months.

from crown to heel than the smallest, a syphilitic contemporary. The epiphyseal ossification line of the smallest fetuses was compared to that of the average-sized and of the longest individuals within each age category. In no case was any abnormality noted. It would appear, then, that while maternal nutrition may be correlated with the length, weight, and well-being of the

fetus and newborn, such a relationship does not usually express itself in recognizable bone changes. The bone lesion of Case 5377 resembles, in some respects, those ascribed to experimental inanition of many types.[4] For want of a better explanation, it is suggested that the intrauterine hypoxemia may have resulted in an inability of the fetus to utilize all of its available nutrients, resulting not only in nanosomia, but also in prenatal athrepsia of bone.

Summary

1. The case history and autopsy findings of a *term* infant weighing 1,400 grams, the child of a lifelong cyanotic woman suffering a cardiovascular anomaly, are presented.

2. A histologically nonspecific lesion, athrepsia of rib and femur, is described.

3. The nanosomia, as well as intrauterine osseous change, is ascribed to fetal hypoxemia.

4. Among 86 fetuses, stillborns and newborns, no qualitative difference in bone formation could be detected between the smallest and largest individuals of a given age group between five and nine months' gestation.

References

1. (a) Burke, B. S., Harting, V. V., and Stuart, H. C.: J. Pediat. **23**: 506, 1943.
   (b) Stuart, H. C.: Federation Proc. **4**: 271, 1945.
   (c) Stuart, H. C.: New England J. Med. **236**: 507, 537, 1947.
2. (a) Warkany, J., and Nelson, R. C.: Arch. Path. **34**: 375, 1942.
   (b) Warkany, J.: J. Pediat. **25**: 476, 1944.
3. Stander, H. J.: Textbook of Obstetrics, 3rd revision, New York, 1945, D. Appleton-Century Company, pp. 131, 132.
4. (a) Levy, B. M., and Silberberg, R.: Proc. Soc. Exper. Biol. & Med. **63**: 355, 1946.
   (b) Levy, B. M., and Silberberg, R.: Proc. Soc. Exper. Biol. & Med. **63**: 380, 1946.
   (c) Silberberg, M., and Silberberg, R.: Arch. Path. **30**: 675, 1940.
   (d) Harris, H. A., Neuberger, A., and Sanger, F.: Biochem. J. **37**: 508, 1943.
   (e) Gillespie, M., Neuberger, A., and Webster, T. A.: Biochem. J. **39**: 203, 1945.

Villafane, Ignacio Z.: Abdominal Puncture in the Diagnosis and Treatment of Acute Pelvic Peritonitis, Prensa méd. argent. **33**: 1446, 1946.

The author, after classifying variations of pelvic peritonitis anent its etiology, pathology, and pathological anatomy, suggests this condition may be not only diagnosed but treated directly through abdominal puncture. He illustrates his principle with a case. After injection of 1.0 c.c. of Novocain, 0.5 per cent, midway on a line between the umbilicus and the superior border of the pubic bone, he introduces a trocar needle slowly into the pelvic region. Seropurulent material is removed for culture. The infected cavity is irrigated with a solution containing 6 to 10 Gm. of a sulfonamide. Single injections of 8 Gm. are repeated every twenty-four to forty-eight hours. Aside from a short interval of slight pain and discomfort the patients show a favorable and relatively rapid clinical response. One graphic temperature record is illustrated. C. E. FOLSOME.

PLASMA VOLUME LATE IN PREGNANCY

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IN A previous paper[1] we reviewed the literature on blood volume in pregnancy and presented values obtained at term and post partum in a group of twenty patients whose plasma volumes were determined by a chromatographic technique applied to the dye-dilution method using Evans blue (T-1824). While there appears to be no doubt about the validity of the contention that a significant increase in plamsa volume occurs as a rule during the course of pregnancy, the suggestion of Thomson and co-workers[2] that plasma volume is appreciably greater at the ninth lunar month than it is at term seemed to us still a debatable issue. Our reasons for thinking so have been given in detail in the previous paper.[1] Caton and others[3] very recently have stated, on the basis of observations in ten patients, that plasma volume decreases significantly "in the latter weeks of pregnancy, averaging 25 per cent of the total increase which had occurred during pregnancy." Certain objections to this conclusion will be indicated later under "Discussion." With the hope that this point might be clarified by further study, we have undertaken to determine plasma volumes in a group of pregnant women approximately four weeks from term and in the same patients just prior to delivery. In addition, plasma volumes were determined in a sizable group of pregnant women at term and in a smaller group of nonpregnant women in the reproductive age period.

Method

The procedure was essentially the same as that already reported,[1] except that a single ten-minute sample of dyed serum (recommended by Gregersen and others[4, 5, 6]) was used instead of the multiple samples which had been necessary to construct a disappearance curve. Instead of preparing our own solution of dye, we used sterile 5 ml. ampules of 0.5 per cent Evans blue obtained from the Warner Institute, New York, calibrating each batch of dye in a Coleman (model 14) spectrophotometer. The dye and syringe were weighed before and after injection,[7] and sufficient blood was obtained to permit determinations in duplicate. The details of the treatment of the dyed serum are as follows: 1.0 ml. of dyed serum is mixed with 0.2 ml. of 0.045 N sodium hydroxide and 1.0 ml. of this mixture is added drop by drop to an adsorption column approximately 2.5 cm. long and 13 mm. in diameter, composed of 1 part magnesium oxide and 20 parts aluminum oxide (reagent grade, Baker and Adamson quality, lot 31, General Chemical Co.). The column is washed with 5.0 ml. of 0.001 N sodium hydroxide and then with 4.0 ml. of an acetic acid—ethanol mixture (1 volume

glacial acetic acid and 9 volumes 70 per cent alcohol). Finally, the dye is removed from the column with 10 ml. of an eluent (10 volumes concentrated hydrochloric acid, 8 volumes of water, and 32 volumes of absolute alcohol). Approximately 1 ml. of eluent is allowed to run through the column to remove the preceding solution and the remainder is collected in a 10 ml. volumetric flask. The recovered solution is diluted to volume with eluent and transmittance is read in a Coleman spectrophotometer at a wavelength of 615 millimicrons, using 19 mm. cuvettes, and with the eluent as a reference solution. Optical density is determined from per cent transmittance, corrected for the original dilution of serum to 1.2 ml., and plasma volume determined by the usual formula[7]:

$$\frac{\text{Mg. dye injected} \times \text{K value of dye}}{\text{Optical density.}}$$

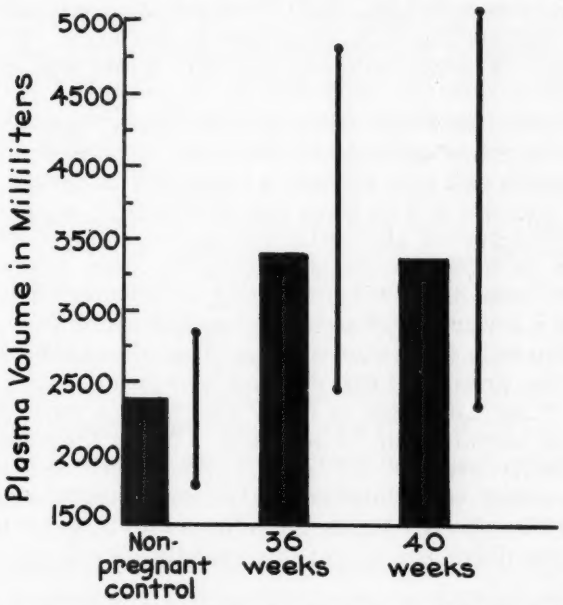

Fig. 1.—Plasma volume in nonpregnant women, in pregnant women a month from term, and in pregnant women at term. The solid columns indicate mean values and the perpendicular lines show the ranges of individual values.

Material

Thirty-three women were used for determination of plasma volume at either thirty-five or thirty-six weeks of gestation, as judged by menstrual history and physical examination as well as by subsequent developments in their pregnancies. Twenty-three of these women were restudied four weeks later, either in the outpatient clinic or, in a few instances, in the hospital just after the onset of labor at term (thirty-nine to forty weeks of gestation). In another group of thirty-three patients plasma volumes were determined at term; a few of these were in early labor but most of them had been admitted to the hospital for induction of labor and were not exhibiting any uterine activity. A final group of ten normal nonpregnant women served as controls to demonstrate the validity of the technique after introduction of the minor modifications as noted above. Since the range of values in these control subjects was the same as that in the previously reported group,[1] the two groups have been merged for purposes of computing the mean and standard deviation of plasma volume in the nonpregnant women.

Results

Controls.—In twenty normal women of childbearing age PV* ranged from 1,820 c.c. to 2,850 c.c. and the mean was 2,385 ± 42† c.c. Thomson and associates[2] found that PV in twenty-eight normal women showed a mean value of 2,324 ± 54 c.c.

Pregnant Women One Month From Term.—Thirty-three patients who were in either the thirty-fifth or thirty-sixth week of pregnancy had plasma volumes ranging from as little as 2,420 to as much as 4,810 c.c., with a mean of 3,372 ± 106 c.c. (Fig. 1). The coefficient of variation for this series is 17.5 per cent, whereas it is only 7.9 per cent for the group of nonpregnant women. When PV is computed in milliliters per kilogram of body weight, the range of values one month from term is from 37.0 to 67.8 with a mean of 50.0 ± 1.5. When surface area is considered, PV in these women ranges from 1.52 to 2.62 liters per square meter and the mean value is 1.96 ± 0.05 liters per square meter. Use of either of these devices for eliminating differences due to variation in body size does not appreciably reduce the coefficients of variation, which still are 16 and 15 per cent, respectively.

Pregnant Women at Term.—(a) Of the twenty-three subjects on whom determinations were repeated at term, seventeen exhibited a lower PV than at the ninth lunar month and only six had a larger PV at term. The greatest drop amounted to 790 c.c. and the smallest was 20 c.c., this latter amount being far below the inherent error of the technique and therefore without significance. Considering these twenty-three patients as an isolated group, the mean PV a month before term was 3,338 ± 111 c.c. and at term 3,251 ± 120 c.c. Of the seventeen showing a lower PV at term, eleven had diminutions in volume which exceeded 200 c.c. but only three showed a loss in excess of 500 c.c.

(b) The entire group of fifty-six subjects studied at term had plasma volumes ranging from 2,320 c.c. to 5,070 c.c., with a mean of 3,316 ± 72 c.c. and a coefficient of variation of 16 per cent. While the mean value at thirty-six weeks was slightly greater (3,372 c.c.), the difference is of no significance (Table I). Converting to milliliters per kilogram, the range is from 34.0 to 75.4, mean 47.6 ± 1.1, whereas the mean value a month prior to term was 50 ml. per kilogram. This difference is not statistically significant. On the basis of

TABLE I. SIGNIFICANCE OF DIFFERENCES BETWEEN MEAN PLASMA VOLUMES AT TERM, AT 36 WEEKS OF GESTATION, AND IN NONPREGNANT SUBJECTS

GROUPS COMPARED	DIFFERENCE BETWEEN MEANS	STANDARD ERROR OF DIFFERENCE	DIFFERENCE DIVIDED BY STANDARD ERROR OF DIFFERENCE	P VALUE	SIGNIFICANT
PV in milliliters					
Controls: 36 weeks	987	114	8.65	.0001	yes
Controls: term pregnancy	930	114	8.14	.0001	yes
36 weeks: term (all cases)	56	128	0.44	.6599	no
36 weeks: term (23 repeats)	87	163	0.53	.5961	no
PV in milliliters per kilogram					
36 weeks: term	2.46	1.83	1.34	.1802	no
PV in liters per square meter					
36 weeks: term	0.056	0.064	0.87	.3843	no

*Throughout the remainder of this paper PV = plasma volume.
†Standard error of mean.

surface area, PV at term ranged from 1.55 to 2.73 L. per square meter and the mean was 1.91 ± .04 L. per square meter, a value which again is not significantly different from that at the ninth lunar month (Table I).

Discussion

In our previous report[1] the average increase in plasma volume at term amounted to 41 per cent. The present series of patients shows a remarkably similar increase amounting to 39 per cent of the average plasma volume for nonpregnant women. At the ninth lunar month the increase in plasma volume amounted to 41 per cent of the normal value, considerably less than the 65 per cent increase shown by Thomson and associates.[2] Caton and his group[3] found an average increase of 49 per cent in their ten patients, using as a standard the mean value thirty days post partum. It has already been pointed out that we could not demonstrate a significantly higher average value for PV at the ninth lunar month, irrespective of the manner in which PV was expressed. However, it must be noted that a majority of this group of patients observed at the ninth and again at the tenth month exhibited a reduction in plasma volume as pregnancy advanced. Likewise, in Caton's[3] study, seven (or perhaps eight) out of the ten subjects showed losses of PV in the last four to eight weeks of pregnancy, but on the other hand two subjects exhibited an *increase* and one (who delivered prematurely) showed no change between the two final determinations made 42 days apart. Their decreases in PV ranged from as little as 40 c.c. to as much as 700 c.c., but in only one instance did the change exceed 500 c.c. In Case 12 the PV was 300 c.c. greater on the fifth antepartum day than it had been fifty-three days ante partum. In Case 17 the PV was 235 c.c. greater on the fourth antepartum day than it had been forty-four days prior to delivery, although it seemingly rose and then fell somewhat in the interim because the *peak* value is recorded for the sixteenth rather than the fourth antepartum day. Caton included this patient with the seven showing a "prelabor" loss of PV, although it seems that changes were occurring in both directions during the final month. In arriving at an average expression of the loss in PV occurring late in pregnancy, Caton excluded his Case 12, presumably because she had mild pre-eclampsia, and also Case 5 because her labor was premature. Thus for eight subjects he obtained a difference of 347 c.c. between the means of the highest antepartum values and the last available antepartum values (0 to 11 days before labor) and stated that this was "significant" because the standard error of the *individual differences* was only 100 c.c. On the other hand, when one uses the more common test for significance which involves the standard errors of the means of the two series of values being compared, it develops that there is no demonstrable significance in the difference between 4,159 c.c. (mean peak antepartum value for eight subjects) and 3,811 c.c. (mean predelivery value). Using Fisher's method of pooled sums of squares and degrees of freedom, the "t" ratio is 1.06, whence the P value is greater than 0.3, suggesting that there are more than 30 chances in a hundred that a difference as great as that observed might be due to an error of sampling. This is so far above the usually accepted 5 per cent level of significance that one could scarcely argue about the meaning of the result.

It is obviously difficult to determine from small samples, even with statistical aid, whether diminution in plasma volume should be considered to be the rule in a preponderant majority of pregnant women, but at least the meager evidence now available suggests that such is the case. Why it should not obtain in *all* cases is somewhat puzzling. On the other hand it seems equally evident that the losses of plasma volume in some individuals are inconsequential as far as cardiac work is concerned, and therefore it may be unwise to make sweeping generalizations about the improvement in cardiac status which is likely to occur during the last lunar month in pregnant women who have heart disease. Apparently one cannot be certain that the individual patient will lose sufficient amounts of intravascular fluid in the last weeks of gestation to produce a favorable influence upon cardiac activity. In general, however, we agree with Hamilton and Thomson[8] when they suggest that there is nothing to be gained by early induction of labor in a cardiac patient since studies of other phases of the circulatory "load" in pregnancy all indicate at least a modest diminution in the total burden during the final three or four weeks of gestation.

Summary

Plasma volume was determined by chromatographic extraction and spectrophotometric determination of Evans blue in pregnant women a month before delivery and at term, as well as in nonpregant control subjects. The mean value at term was not significantly lower than that at the the thirty-sixth week. However, a majority of the subjects showed lower individual values at term but very few exhibited a loss in volume which might have been of clinical importance. The relationship of this finding to the management of cardiac disease in pregnant women is discussed briefly. A previously reported mean increase of 40 per cent in plasma volume during pregnancy is confirmed in this larger series of observations.

References

1. McLennan, C. E., and Thouin, L. G.: Am. J. Obst. & Gynec. **55**: 189, 1948.
2. Thomson, K. J., Hirsheimer, A., Gibson, J. G., II, and Evans, W. A. Jr.: Am. J. Obst. & Gynec. **36**: 48, 1938.
3. Caton, W. L., Roby, C. C., Reid, D. E., and Gibson, J. G., II: Am. J. Obst. & Gynec. **57**: 471, 1949.
4. Gregersen, M. I.: J. Lab. & Clin. Med. **29**: 1266, 1944.
5. Noble, R. P., and Gregersen, M. I.: J. Clin. Investigation **25**: 158, 1946.
6. Hopper, J., Jr., Tabor, H., and Winkler, A. W.: J. Clin. Investigation **23**: 628, 1944.
7. Price, P. B., and Longmire, W. P.: Bull. Johns Hopkins Hosp. **71**: 51, 1942.
8. Hamilton, B. E., and Thomson, K. J.: The Heart in Pregnancy and the Childbearing Age. Boston, 1941, Little, Brown and Company.
9. Fisher, R. A.: Statistical Methods for Research Workers, ed. 5, Edinburgh and London, 1934, Oliver and Boyd, Ltd.

NECROSIS AND DETACHMENT OF THE CERVIX DURING LABOR

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NECROSIS and partial or complete detachment of the cervix occur as a rare complication during labor. There have been fifty-five cases reported since Scott published the first description in 1821. The incidence is higher as evidenced by the discussers who usually relate an unpublished case or two. Ingraham and Taylor published the most recent case report and provided a scholarly analysis of the preceding cases. Five cases of spontaneous necrosis and detachment occurred in 56,884 deliveries at the New York Hospital from September, 1932, to December, 1948, an incidence of approximately 1:11,000.

Case Reports

CASE 1.—Year 1934. This 33-year-old white, para 0, gravida i, with normal pelvic measurements, had a prolonged labor of 56 hours. The membranes ruptured spontaneously after 36 hours of labor. The vertex was at the spines in left occipitotransverse position. Two hours later the anterior lip of the cervix was noted to be edematous. The fetal heartbeat was lost during the spontaneous delivery of a 3,020 gram deadborn infant. The blood loss was 300 c.c.

Immediately after the delivery of the placenta the anterior lip of the cervix was noted to be edematous, necrotic, and attached by only a thin strand of tissue. This was ligated and removed. The fragment of cervix, which measured 6 by 2 by 2 cm., was hemorrhagic and necrotic. Microscopically the blood vessels were distended and there was extravasation of blood into the connective tissue. There was postpartum fever for five days due to intrauterine infection. Twelve days after delivery the cervix was noted to be badly torn, eroded, and deficient in its anterior lip.

Two years later, in 1936, the cervix was clean and well epithelized, but the posterior lip protruded 1 cm. beyond the anterior lip. An uneventful full-term spontaneous delivery occurred at this time after nine hours of labor.

CASE 2.—Year 1938. This 27-year-old white para i, gravida ii, had a contracted pelvis with an obstetrical conjugate of 11.5 cm. X-ray pelvimetry revealed a platypelloid pelvis, the obstetrical conjugate measuring 9.5 cm. An extraperitoneal cesarean section of Latzko type had been performed in the first pregnancy (1937) after forty-eight hours of labor, the infant weighing 4,940 grams. The membranes ruptured after twenty hours in the present pregnancy. A forceps delivery was decided upon when fetal distress developed as the caput came into view. Immediately prior to delivery the anterior lip of the cervix was found to have separated and was attached only on the right side. A 4,510 gram infant was delivered in right occipitotransverse position by forceps. The necrotic cervical lip, which measured 5 by 3 by 1 cm., was ligated at its base and removed. A postpartum hemorrhage of 1,000 c.c. occurred. There was puerperal infection for eleven days, retention of urine, and cystitis. Sixteen days after delivery the anterior lip was noted to be granulating and a sloughing ulcer was present on the anterior vaginal wall. Twenty-one days after delivery a vesicovaginal fistula developed at this spot. This was successfully repaired six years later in 1944. The cervix at this time was lacerated anteriorly and everted. Ten years later (1949) the patient was delivered by elective low-flap cesarean section in another hospital.

CASE 3.—Year 1938. This 27-year-old white, para 0, gravida i, had a flat pelvis, the obstetrical conjugate being 11.75 cm. The membranes ruptured after twenty hours of labor. Position was right occipitoposterior. Six hours later and one hour prior to delivery, a dark red mass, 4 by 4 by 1 cm., was noted at the vaginal orifice (Fig. 1). A spontaneous delivery of a 3,690 gram infant occurred after the edges of this mass had been clamped and ligated. This necrotic fragment of cervix measured 6 by 3 by 2 cm. and showed edema, extravasation of blood, and degeneration. The postpartum course was afebrile and complicated only by the presence of residual urine. Six weeks after delivery the anterior lip of the cervix was shortened, but healed. No subsequent deliveries have occurred.

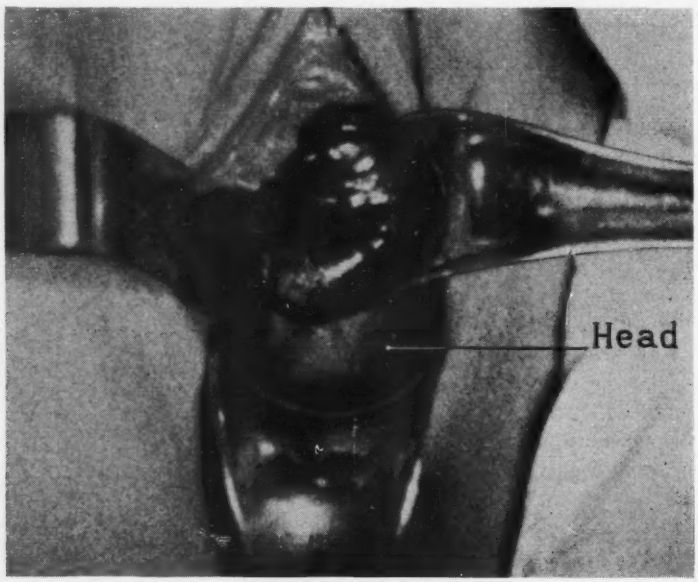

Fig. 1.—The necrotic anterior lip of the cervix immediately prior to delivery.

Fig. 2.—The entire detached necrotic fragment of the cervix. It is discolored, hemorrhagic, and congested. (×1.)

CASE 4.—Year 1948. This 36-year-old white para i, gravida ii, had had a previous uneventful spontaneous delivery in 1939. The pelvis was normal, with an obstetrical conjugate of 12.5 cm. The anterior lip of the cervix showed marked edema after thirteen hours of labor. Position was right occipitotransverse. One and one-half hours prior to delivery, cervical detachment was noted. After nineteen hours of labor a 3,360 gram infant was delivered by the combined use of Barton and DeWees forceps. Blood loss was 300 c.c. The detached part of the cervix extended from 6 o'clock, in clockwise fashion, to 2 o'clock. It was clamped and cut at the border of the normal cervix and sutured with No. 00 chromic

catgut. The segment measured 13 by 2 by 1 cm. (Fig. 2). The baby died on the fifth day of intracranial hemorrhage. Several days after delivery the cervix had a jagged border except from 2 to 6 o'clock. No further follow-up was possible.

CASE 5.—Year 1948. This 28-year-old white para 0, gravida i, had a contracted pelvis. Pelvimetry showed a gynecoid pelvis with anthropoid tendencies. The obstetrical conjugate was 11.25 cm., while the transverse diameter of the inlet was 12.25 cm. The membranes ruptured after twenty hours of labor at which time the cervix was firm, thick, and well applied to the vertex in left occipitotransverse position. Vaginal examination after fifty-seven hours of labor revealed a band running across the cervix from 2 to 8 o'clock. This was ruptured with the immediate attainment of full dilatation. Low forceps delivery of a 3,530 gram infant was performed. The infant showed evidence of intracranial injury and after two months of hospitalization was discharged well. Blood loss was 400 c.c. The band measured 6 by 3 by 1 cm. and showed infection and necrosis (Fig. 3). The postpartum period was marked by six days of fever due to a right broad ligament hematoma which most likely represented an incomplete uterine rupture. There was also urinary tract infection. One year after delivery the anterior lip of the cervix was absent, so that the posterior lip protruded 2 cm. beyond it. The uterus was anterior and there were no parametrial masses.

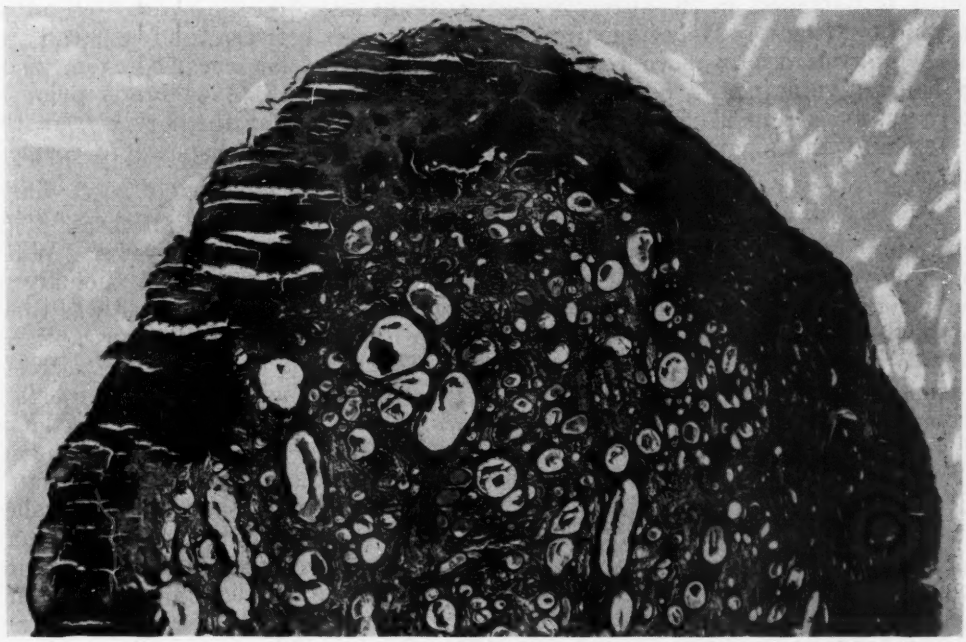

Fig. 3.—Cross section of the necrotic lip. Note the extravasation of blood, the dilatation of all the blood vessels, and the poor preservation of the tissue. (×15.)

CASE 6.—Year 1936. This 31-year-old white para 0, gravida ii, had a normal pelvis, the obstetrical conjugate being 12 cm. Vaginal examination after thirty-two hours of labor revealed an edematous anterior lip, measuring 3 cm., showing early necrosis and discoloration. Three hours later Dührssen's incisions were made and a midforceps delivery performed because of fetal distress. When the cervical incisions were sutured, the anterior lip was thought to be viable and hence was preserved. One month after delivery the cervix appeared normal.

Cases 1 through 5 illustrate necrosis and detachment of the cervix, while Case 6 represents the necrosis which does not progress to irreversible tissue destruction and spontaneous detachment of the cervix.

Pathology

The detached cervix was examined in each case. Gross examinations of the fragments revealed them to be discolored, necrotic, edematous, with areas of hemorrhage and passive congestion (Fig. 2). Microscopic examination showed distention of blood vessels, extravasation of blood, edema, and polymorphonuclear leucocytes (Fig. 3). Cervical glands and squamous epithelium were present in all cases. Two of the cervices showed decidual changes in the stroma. There were varying degrees of necrosis even in the same specimen.

Discussion

Three of our patients were primigravidas. Their ages ranged from 27 to 36, averaging 30.5 years. Two of the pelves were normal, while the remaining three showed contraction in the anteroposterior diameters. An effort was made to obtain pelvic x-rays in all these patients, but it was successful in only two patients. One of these had a true flat pelvis and the other had a gynecoid pelvis with anthropoid elements. Detachment occurs most commonly in the pelvis which is flattened in its anteroposterior diameters either by platypelloid or android tendencies. Hence, compression of the cervix between the fetal head and the symphysis occurs more readily. The duration of labor varied from 20 to 58 hours, averaging 39 hours. Membranes ruptured 17 to 44 hours prior to delivery, averaging 27 hours. The membranes may buffer the cervix from the vertex and the symphysis, hence their early rupture predisposes to cervical necrosis.

It was the anterior lip which was transversely lacerated in all cases. This then hung from its partial attachment to the posterior lip of the cervix. When this was felt in one patient it was first interpreted as a congenital anomaly of the cervix. Only partial separation occurred in all cases. In no case was there complete detachment of the cervix. The depth of the posterior pelvis and the curve of the sacrum protect the posterior lip of the cervix from pressure necrosis. Edema was noted in three of the anterior lips prior to their detachment. This is probably the earliest sign of interference with the blood supply. Not all edematous cervices proceed to necrosis and detachment, but the palpation of an anterior lip which is markedly edematous and congested, warrants vaginal examination to determine the condition of the lip. The edematous lip may be pushed over the vertex in some patients when the cervix is fully dilated, hence eliminating further pressure. If the lip remains unchanged or becomes more congested prior to full dilatation of the cervix, delivery by cesarean section or Dührssen's incisions may be considered. The detachment was noted during the first stage of labor in three patients (four hours, one and one-half hours, and just prior to delivery, respectively). It was noted in the second stage in one and after delivery of the placenta in the last patient. Position was left occipitotransverse in two patients; right occipitotransverse, in two others, and right occipitoposterior in the last. No observations were made regarding synclitism. The babies averaged 3,600 grams, ranging from 3,020 to 4,510 grams. Fetal mortality was 40 per cent; one infant was born dead, while the other died during the neonatal period. One other had a transient intracranial injury without sequelae; the fourth had an Erb's palsy. Only one infant was normal. The high incidence of fetal death and trauma is in conformity with the recorded analyses. It suggests such a close approximation of the fetal diameters to the pelvic diameters that while cephalopelvic disproportion was not present, the fetus had no room for accommodation and the obstetrician had none for maneuver.

The bladder is also subjected to pressure necrosis. The effects of this were manifested by urinary retention in three patints and by a vesicovaginal fistula in one other. Here necrosis results in localized fistula formation without detachment, as occurs in the cervix.

Blood loss was not excessive. Only one patient had a postpartum hemorrhage of 600 c.c. The necrosis destroys the lumina of the vessels with thrombosis, hence the lack of hemorrhage. The partially separated necrotic band of cervix can be cut from the cervix without the occurrence of bleeding. It is not necessary to ligate the base.

The transverse cervical laceration extended up into the lateral side of the lower uterine segment in one case. There was incomplete uterine rupture and broad ligament hematoma. This gradually absorbed during several weeks of observation.

Three patients had fever, maintaining temperatures over 38.0° C. for five, six, and eleven days, respectively. Two patients were afebrile. Two of these patients were observed in subsequent pregnancies. One delivered spontaneously without event two years after cervical detachment. The other was delivered by elective transverse cesarean section eleven years afterward, because of relative cephalopelvic disproportion in a woman with a successful repair of a vesicovaginal fistula, a previous cesarean section, and a previous necrosis and detachment of the cervix.

The five cervices were not thought to be unusually rigid or exceptionally long, though both of these factors have been suggested as predisposing to cervical necrosis. The mechanism of cervical necrosis and detachment is outlined in Table I. Predisposing factors such as prolonged labor with early rupture of the membranes in a flat or contracted pelvis lead to the trapping of the anterior lip of the cervix between the vertex and the symphysis. The cervix becomes congested and edematous. Relief of pressure on the cervix by delivery or releasing of the trapped cervix permits return of the cervix to its original state. Simultaneously, pressure on the anterior bladder wall causes congestion, edema, and necrosis with the possible late development of a vesicovaginal fistula. Persistent ischemia of the cervix leads to necrosis without detachment as in Case 6. Further ischemia results in the formation of a cervicovaginal fistula as in the three patients who still showed attachment of the necrotic fragment to both sides of the cervix (Cases 3, 4, and 5). The process may arrest here or proceed to separation of one of these bridges of tissue as in the other two patients (Cases 1 and 2). This usually permits delivery; therefore, separation of both margins rarely occurs. Once necrosis has occurred the process is irreversible, although it may stop at formation of a cervicovaginal fistula without detachment.

TABLE I. MECHANISM OF CERVICAL NECROSIS AND DETACHMENT DURING LABOR

Reversible.—
1. Long labor
2. Late in the first stage
3. Pelvis usually contracted in anteroposterior diameter
4. Early rupture of membranes
5. Pressure of the anterior lip of the cervix between the vertex and the symphysis
6. Edema of the cervix
7. Congestion of the cervix
Irreversible.—
8. Necrosis of the cervix
9. Formation of a cervicovaginal fistula
10. Partial spontaneous detachment of the necrotic cervix
11. Complete spontaneous detachment of the necrotic cervix

Although all of these detachments occurred spontaneously, it is conceivable that trauma by forceps or other instruments might cause detachment of the cervix, regardless of previous necrosis. Complete annular detachment has been described, but has not been encountered in this series. All the cases were spontaneous, partial necrosis and detachment of the cervix.

Various terms are used, to wit, spontaneous amputation of the cervix, circular amputation, annular detachment, or transverse rupture of the cervix. "Circular amputation" or "annular detachment" seem inappropriate, since the detachment is so rarely complete. "Necrosis and detachment of the cervix during labor" is the most apt term inasmuch as it describes the mechanism and the pathological findings.

One additional patient passed a cervical polyp which was thought to represent a detachment of the cervix until inspection of the cervix proved it to be intact and histological study proved the presence of a polyp.

The mechanism of cervical necrosis and detachment is outlined in Table I. The pelvic architecture of patients with spontaneous necrosis of the cervix should be studied by x-ray.

Summary

Five cases of spontaneous necrosis and detachment of the cervix during labor are reported. Long labor, ruptured membranes, and a flat or contracted pelvis are predisposing factors. Pathogenesis is suggested as proceeding from pressure of the anterior lip of the cervix between the vertex and the symphysis, to congestion and edema and finally necrosis of the cervix. Then a cervicovaginal fistula forms with spontaneous detachment of the necrotic cervix.

Prevention consists in the releasing of pressure on the trapped anterior lip of the cervix prior to the appearance of irreversible necrosis.

Reference

1. Ingraham, C. ., and Taylor, E. S.: Am. J. Obst. & Gynec. **53**: 873, 1947.

Farris, Edmond J.: Temperature Compared With Rat Test for Predication of Human Ovulation, J. A. M. A. **138**: 560, 1948.

The author reports observations made on twenty-seven women. Basal body temperatures were taken rectally. The occurrence of ovulation was detected by the reaction of the ovary of the immature white rat to the urine of the patient. The first month is utilized as a control and no attempt at conception is advised during this month. The control month tells whether ovulation occurs and when it takes place in relation to the duration of the cycle and whether the reaction is normal or abnormal. During the following month, intercourse is advised or artificial insemination is performed on the last day of the reaction if the reaction is normal. Twenty-three of the twenty-seven women had their ovulation timed during the month that conception occurred. Sixteen of the women became pregnant by coitus and nine by single inseminations (four by anonymous donors and five by homologous donors). Of the twenty-seven conceptions, 41 per cent occurred before there was any change in basal body temperature; 7 per cent took place after the rise; 15 per cent occurred as the temperature dropped; 37 per cent occured during the rise. These observations indicate that the changes in basal body temperature in most instances are of such a nature that they do not permit an accurate timing of ovulation. William Berman.

THE EFFECTS OF SEDATION ON FALLOPIAN TUBAL MOTILITY

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THE physiology of the Fallopian tubes has long been the subject of much laboratory and clinical investigation. Peristalsis and contractions of the Fallopian tubes have been demonstrated both in isolated strips of the excised tube[1] and in the extirpated intact surviving genitals.[2] The presence of spontaneous contractions and peristalsis have also been seen and photographed through an abdominal window in unanesthetized animals.[3]

Extensive studies have clearly demonstrated the cyclic influence of ovarian function on the spontaneous contractions of the Fallopian tubes in laboratory animals[4] and in the human being.[5] The effects of drugs on tubal function have been studied by many investigators on laboratory animals[6, 7] and on the extirpated human genitals.[8] The pharmacological response of the intact human Fallopian tube in vivo, however, has received little attention.

The present clinical investigation is an attempt to establish the reactions of the human Fallopian tubes to various sedative drugs and to determine their clinical value in diagnostic and therapeutic uterotubal insufflation. Patients attending the sterility clinic and many of those admitted to the gynecological ward for surgical procedures were subjected to repeated uterotubal insufflation tests. In each case a careful control test was performed before attempting to evaluate the effect of any drug. The methods of administration of the drugs and the details of testing will be discussed individually later.

Method

The apparatus used was the standard Rubin model made by Becker. All physical factors in the machine were kept constant throughout the tests. The gas was delivered under a pressure of 15 pounds and at a constant rate of flow of 60 c.c. of carbon dioxide per minute. The pressure and rate of flow were checked before starting any tests. The cervix was exposed, cleansed, and painted with Merthiolate. It was then grasped with a tenaculum and a cannula introduced into the cervical canal. A few moments were allowed to pass until the patient was quiet and at ease before the flow of gas was started. Proper air-tight obturation of the cervix was obtained by slight pressure of the rubber acorn tip of the cannula against the cervix and slight traction upon the tenaculum. Care was taken not to displace the uterus from its normal position in the pelvis. Such a procedure could possibly stretch the mesosalpinx and tube, giving anomalous kymographic tracings.

Material

A group of sixty-seven women was selected to determine the effects of three different types of sedatives on Fallopian tubal activity. In each case a control insufflation was performed and a kymographic recording of the tubal contractions

was obtained for five to ten minutes. The patients were then returned to bed and were given an adequate dose of the sedative to be tested. An hour later they were again subjected to a tubal insufflation test and the kymographic recordings were compared to the control tracings.

A. Twenty-seven women were selected as controls for repeated insufflations without the administration of any drugs. The tests were conducted as outlined above. Comparison of the kymographic recordings revealed that in eighteen cases the initial pressure of tubal patency in the repeat insufflation was the same or lower than that of the initial test. The general pressure level at which tubal contractions occurred regularly was practically the same and the amplitude was not appreciably altered. In two cases there was an increase of the pressure at which tubal patency occurred with slight increase in the amplitude of the tubal contractions.

B. A group of seventeen women was insufflated to determine the effects of morphine sulfate. After a trial insufflation, ¼ grain of morphine sulfate was given subcutaneously and the patients were insufflated again one hour later. It is of extreme interest to observe the results obtained despite the fact that the patients' ages varied from 24 to 60 years and in three cases menstruation had ceased ten years previously. In twelve cases the initial pressure at which tubal patency was present was increased from 10 to 80 mm. Hg and in one case nonpatency occurred following morphine administration. The average increase in tubal patency pressure was 40 mm. Hg. In five patients there was a decrease of tubal patency pressure of from 10 to 30 mm. Hg. The general level of pressure at which regular tubal contractions occurred was increased in eleven patients, remained the same in three patients, and decreased slightly in three.

The most striking changes were seen in the consistent increase in amplitude of the tubal contractions. The amplitude of the contractions increased in sixteen of the seventeen patients and remained the same in one, a 60-year-old woman. The average increase in amplitude of contractions was 30 mm. Hg. The greatest changes was that seen where the amplitude of contractions rose from a level of 10 to 20 mm. Hg to that of 70 to 80 mm. Hg. In two of the three menopausal patients there was a marked increase in the amplitude of contractions. In all cases, with the increase in amplitude of contractions there was an increase in the duration of each contraction, some contractions lasting as long as ninety seconds (Figs. 1 and 2).

C. A group of fifteen patients between the ages of 24 to 48 years was insufflated to determine the effects of Demerol. Each patient had a control insufflation and then was given 100 mg. of Demerol by hypodermic. The patients were insufflated again one hour later. The initial pressure at which tubal patency was present was increased in seven patients, decreased in six patients, and remained the same in two patients. The average increase in the tubal patency pressure in seven cases was 35 mm. Hg, while the average decrease in the six patients was 30 mm. Hg. The general level of pressure at which regular tubal contractions occurred was increased in nine patients, decreased in three patients and remained the same in three patients. In one case the increase in the general level was as high as 60 mm. Hg but as a rule the general increase of level averaged 20 mm. Hg. The average decrease in pressure in three cases was 10 mm. Hg. The most striking changes were again seen in the change of amplitude of tubal contractions. The amplitude of contractions was increased in ten cases, remained the same in two cases and in three cases a kymographic curve of tubal spasm was obtained. In the three latter cases all tubal contractions were obliterated. The average increase in amplitude of tubal contractions was 20 mm. Hg (Fig. 3).

D. A group of fifteen women between the ages of 23 and 47 years was insufflated to determine the effects of Nembutal. Each patient had a control insufflation and was then given 3 grains of Nembutal by mouth. The patients were again insufflated one hour later. The initial pressure of tubal patency was increased in ten patients, decreased in three patients, and remained the same in two patients. The average increase in tubal patency was 25 mm. Hg. The general level at which tubal contractions occurred regularly was increased in six patients, remained the same in five patients, and decreased in four patients.

S. E., AGE 33, L.M.P. 9-11-48

9-21-48 A B

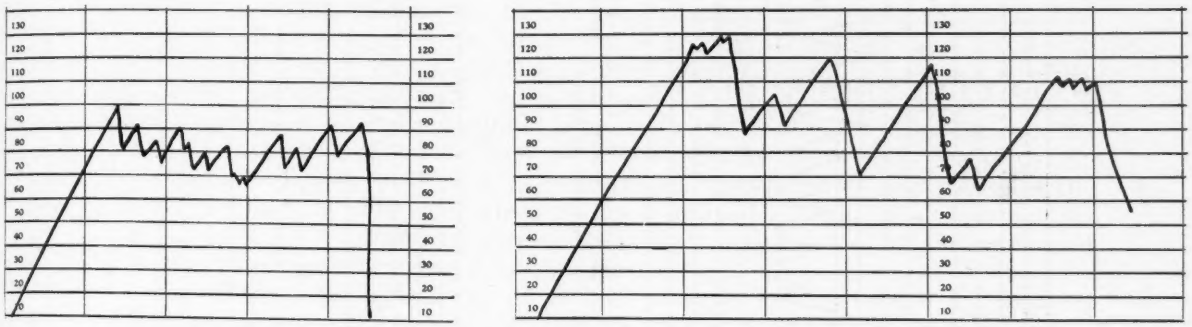

Fig. 1.—*A*, Control uterotubal insufflation test performed on a 33-year-old patient on the tenth day of the menstrual cycle.

B, Insufflation curve obtained one hour after the hypodermic injection of ¼ grain morphine sulfate. Note the increased pressure level of tubal patency and the marked increase in amplitude of the tubal contractions.

C. G., AGE 55, L.M.P. 1944

5-18-48 A B

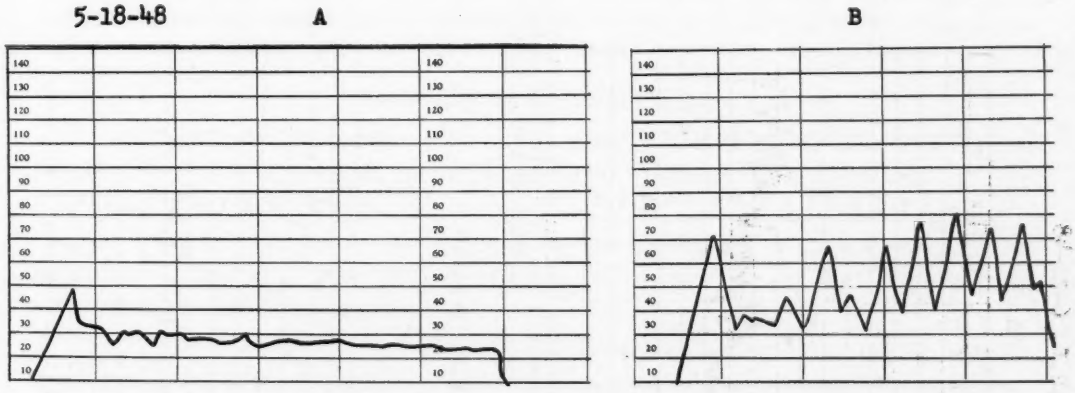

Fig. 2.—*A*, Control uterotubal insufflation test performed on a menopausal patient. Tubal patency is present at a low pressure and tubal contractions are practically absent.

B, Insufflation curve obtained one hour after the hypodermic injection of ¼ grain morphine sulfate. Note the increased pressure level of tubal patency and the high amplitude of the tubal contractions.

The average increase in pressure level was 30 mm. Hg, while the average decrease was 10 mm. Hg. The amplitude of contractions was increased in seven patients, remained the same in six patients, and decreased in two patients. The average increase in amplitude of contractions was 15 mm. Hg. In one case tubal spasm occurred and tubal contractions were entirely obliterated (Fig. 4).

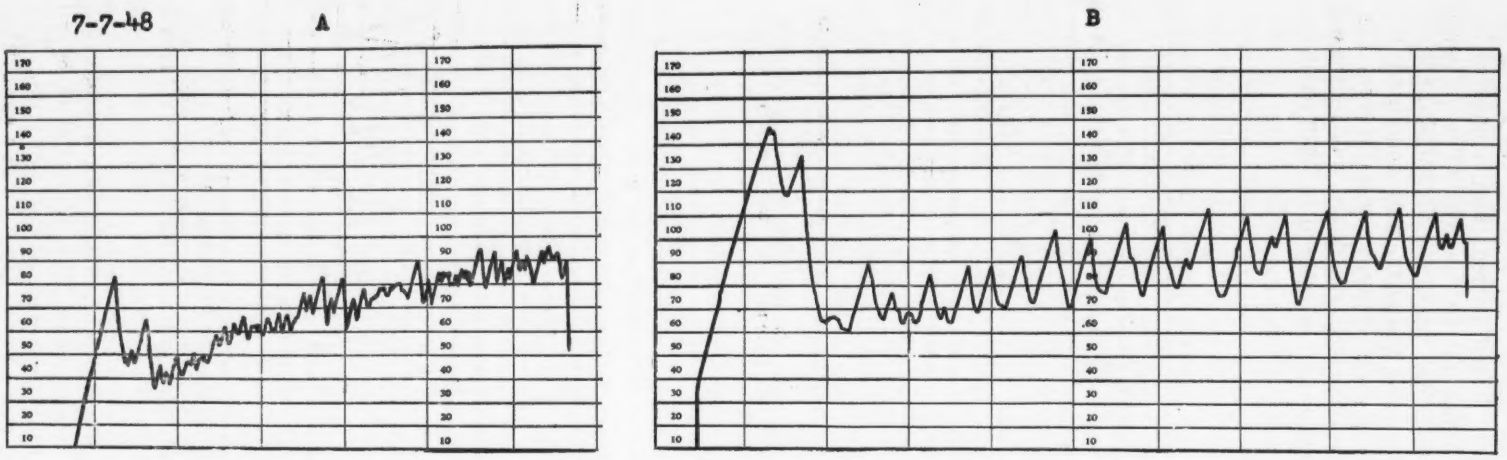

Fig. 3.—*A*, Control uterotubal insufflation test on a 40-year-old woman on the fifteenth day of the menstrual cycle. *B*, Insufflation curve obtained one hour after the administration of 100 mg. of Demerol. Note the increased pressure level of tubal patency and the marked increase in amplitude of tubal contractions.

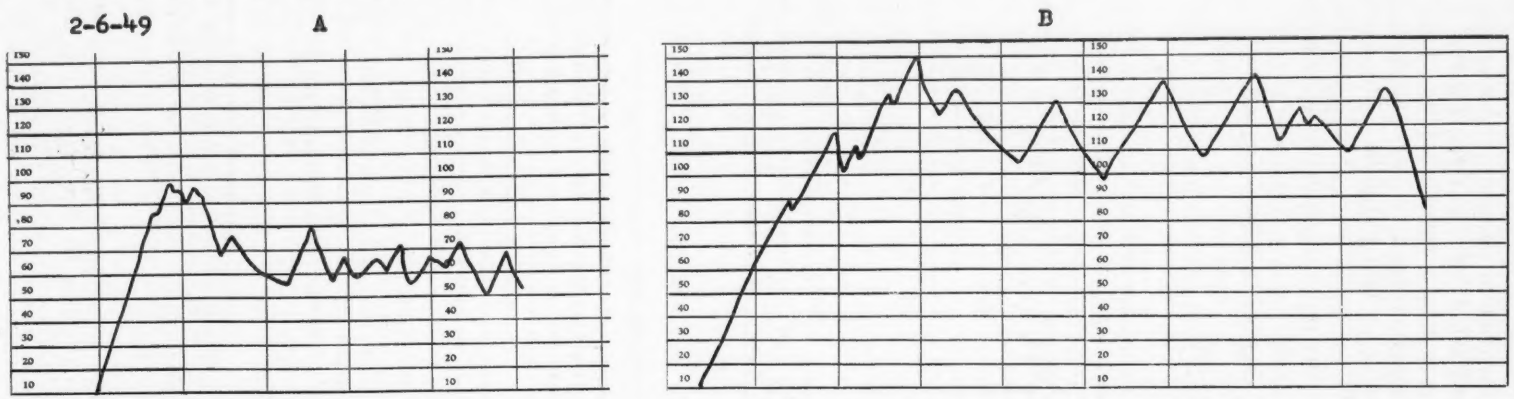

Fig. 4.—*A*, Control uterotubal insufflation test performed on a 28-year-old patient on the tenth day of the menstrual cycle. *B*, Insufflation curve obtained one hour after the administration of three grains of Nembutal. Note the increases in the pressure level of tubal patency, the general pressure level of the curve, and the amplitude of tubal contractions.

Comment

The foregoing data reveal several interesting facts. The effects of morphine sulfate on the smooth-muscle wall of the Fallopian tube is similar to that found in many other organs of the body. Morphine sulfate stimulates smooth-muscle tone in the bronchi, stomach, pyloric sphincter, small and large intestine, biliary tract, sphincter of Oddi, ureter, urinary bladder, and bladder sphincter muscle.[9-12] In the Fallopian tube it is seen that morphine sulfate definitely increased the amplitude of tubal contractions in sixteen of the seventeen women tested. In twelve cases it increased the pressure level of initial tubal patency and in eleven cases it increased the general level at which regular tubal contractions occurred.

In general, Demerol, unlike morphine sulfate, has demonstrated effects which resemble the action of atropine on the pupil, heart, and bronchi and has spasmolytic effects similar to papaverine on the bronchi, intestines, and blood vessels. The stomach, pylorus, small and large intestine, ureter, and gall bladder are usually relaxed by Demerol. The action is partly anticholinergic and partly direct depression of smooth-muscle activity.[13] The effect of Demerol on the Fallopian tubes does not seem to show a spasmolytic action. On the contrary, there was an increase in the initial pressure of tubal patency in one-half of the number of patients and an increase in the amplitude of the tubal contractions in two-thirds of the number of patients tested. It had no effect on the amplitude of contractions in two of the fifteen patients.

The effects of barbiturates on smooth muscle have not been as clear-cut as that of morphine sulfate or Demerol. In the doses used clinically there is a decrease of tone and of the amplitude of contractions of the gastrointestinal muscles. The uterus, however, has been shown to be resistant to the depressant effect. It does not significantly reduce the uterine contractions in labor.[14] The effect on the Fallopian tubes demonstrates no spasmolytic action. On the contrary, in two-thirds of the number of patients tested there was an increase in the initial pressure of tubal patency and in slightly less than one-half of the number of patients tested there was an increase in the general tubal tone and the amplitude of contractions. In less than one-third of the number of patients was there any spasmolytic action demonstrated.

Summary and Conclusions

1. A group of sixty-seven patients was subjected to uterotubal insufflation to determine the effects of morphine sulfate, Demerol, and Nembutal on the Fallopian tubal musculature.

2. A control group of twenty women was subjected to repeated tubal insufflations. Repeated tests do not cause tubal spasm nor do they increase the amplitude of the tubal contractions.

3. Morphine sulfate consistently stimulates the contractions of the smooth muscle of the human Fallopian tube.

4. Demerol and Nembutal in general stimulate rather than depress the smooth muscle of the human Fallopian tube.

5. The use of sedatives such as morphine sulfate, Demerol, and Nembutal is not of clinical value in overcoming increased tonus or spastic closure of the Fallopian tubes.

References

1. Kehrer, E.: Arch. f. Gynäk. 81: 160, 1907.
2. Gunn, J. A.: Proc. Roy. Soc., London 87: 551, 1913-14.

3. Rubin, I. C., and Davids, A. M.: Moving Picture Demonstration, 1940.
4. Wimpfheimer, S., and Feresten, M.: Endocrinology **25**: 91, 1939.
5. Davids, A. M.: Am. J. Obst. & Gynec. **56**: 655, 1948.
6. Kok, F.: Med. Klin. **21**: 1694, 1925.
7. Davids, A. M., and Bender, M. B.: Am. J. Physiol. **129**: 259-263, 1940.
8. Gunn, J. A.: Proc. Roy. Soc., London **87**: 551, 1913-14.
9. Veach, H.: J. Pharmacol. & Exper. Therap. **61**: 230, 1937.
10. Kruger, H.: Physiol. Rev. **17**: 618, 1937.
11. Butsch, W. L., McGowan, J. M., and Walters, W. W.: Surg., Gynec. & Obst. **63**: 451, 1936.
12. Okenblad, N. F., Carlson, H. E., and Simon, J. F.: J. Urol. **33**: 356, 1935.
13. Yonkman, F. F., Noth, P. H., and Hecht, H. H.: Ann. Int. Med. **27**: 7, 1944.
14. Gruber, C. M., and Brundage, J. T.: J. Pharmacol. & Exper. Therap. **60**: 439, 1937.

Ingelman-Sundberg, Axel: Uterovesical Fistula Following Therapeutic Abortion, Gynecologia **126**: 274, 1948.

An operation is reported in one case of a uterovesical fistula following a therapeutic abortion. (The latter was done by vaginal hysterotomy at about 6 months' gestation.)

The method consists of suturing the fistula and then dividing the pubococcygeus muscles and thus obtaining two anterior flaps (attached to symphysis) and two posterior flaps (attached to the region of the coccyx). The two anterior flaps are crossed and sutured with silk to the cervix. The posterior flaps are sewed in the mid-line in front of the rectum with heavy catgut.

Follow-up seventeen days later showed complete healing and the patient symptom free.

EUGENE N. SCADRON.

Bastiaanse, V. Bouwdijk: Treatment of Carcinoma of the Cervix, An. brasil. de ginec. **26**: 237, 1948.

Bastiaanse, Professor of Obstetrics and Gynecology at the University of Amsterdam, reports on his experience in the management of 591 carcinoma of the cervix cases in a lecture at the Gynecological Institute of the University of Brazil, Rio de Janeiro. He found that only 15 per cent of the admitted cases may be treated surgically while radium therapy is employed in the remaining 85 per cent.

Between Aug. 15, 1938, and July 1, 1948, 591 patients were admitted. In 278 cases, or 47 per cent, a radical vaginal operation was performed. Seven patients, 2.52 per cent, were in the primary surgical mortality group but the preclusion of adequate preoperative care by war conditions in Holland was claimed to be responsible for this higher mortality because since 1941 only one patient has been lost, 0.5 per cent.

The author could not offer data on his five-year cures because his files were lost during the bombing of Rotterdam. He performed the Schauta-Stoeckel vaginal operation 109 times in Amsterdam, or in 42.58 per cent of 526 cases admitted from Aug. 15, 1938, to Jan. 1, 1948. The cure rates of these cases which could be found were Grade I, 63 patients operated upon; 34 cured after five years, or 54 per cent; Grade II, 44 patients operated upon, 21 were cured after five years, or 47.7 per cent, or a total of 51 patients cured (51.4 per cent) for Grades I and II.

C. E. FOLSOME.

AN ANALYSIS AND EVALUATION OF VINBARBITAL SODIUM FOR OBSTETRIC AMNESIA AND ANALGESIA

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(From the Wichita Foundation of Medical Research)

WITH the myriad of drugs which have been recommended for obstetrical analgesia and amnesia, a certain amount of confusion and indecision has arisen as to the most satisfactory form of medication. As a result of this indecision some obstetricians have finally eliminated any routine form of analgesia. The writer feels that an obstetric analgesic and amnesic agent should meet certain qualifications. These qualifications might be listed as follows:

1. There must be an adequate margin of safety for the mother causing no respiratory or circulatory depression.
2. It should not delay or prolong any stage of labor and should not predispose to postpartum complications such as hemorrhage, thrombosis, etc.
3. It should have no depressing effect on the infant.
4. It should provide analgesia with a minimum amount of excitation. If amnesia can be obtained in addition to the above, the agent becomes even more satisfactory from the patient's standpoint.

Many forms of medication which have been used in the past will provide analgesia and amnesia, but some have the disadvantage of prolonging labor and many cause depression of the newborn.

As a result of favorable reports by Bernstine and Prince[1] and Lewis[8, 9] on the use of vinbarbital sodium* for obstetric amnesia and analgesia, the author decided to use it as a routine medication until it had been given a fair trial. For the past twenty months it has been used on all obstetrical patients. The information for this report was obtained from the hospital records prepared by hospital personnel who did not know that this analysis would be made. In an attempt to compare vinbarbital sodium with other types of medication, 88 unselected cases in which various other forms of medication were employed are analyzed and compared with 213 unselected, consecutive cases in which vinbarbital sodium was used. An additional 14 cases in which no medication or anesthesia was used are reported in an attempt to compare vinbarbital sodium cases with so-called "natural labor."

Material

Patients are divided into two groups. Group One consisted of those patients receiving various forms of barbituric acid derivatives and other obstetric analgesic agents with and without scopolamine. Group Two consisted of those patients receiving vinbarbital sodium orally and intravenously or a combination of both with and without scopolamine. The patients were grouped as follows:

Group I	88 cases
Primiparas	42 (37.7%)
Multiparas	46 (62.3%)
Group II	213 cases
Primiparas	100 (46.9%)
Multiparas	113 (53.1%)

*Vinbarbital sodium is the nonproprietary name for sodium 5-ethyl 5-(1-methyl-1-butenyl) barbiturate. It is distributed under the name of Delvinal. The material used was provided through the courtesy of the Medical Research Division, Sharpe & Dohme, Inc., Philadelphia, Pa.

The youngest patient in the series was 15 years of age and the oldest was 45 years. The distribution according to age group is shown in Table I.

TABLE I

AGE IN YEARS	PERCENTAGE OF CASES
15-20	30
21-25	32
26-30	23
31-35	13
36-40	2
45	1 case

Presentation was as follows: 287 cephalic and 16 breech. Two sets of twins were included in the series. Distribution of these presentations according to position is shown in Table II.

TABLE II

POSITION	GROUP I	GROUP II
Left occipitoanterior	61	150
Right occiptioanterior	18	43
Left occipitoposterior	1	3
Right occipitoposterior	3	6
Breech	5	11
Face	0	1
Brow	0	1

Table III shows an analysis of the cases according to the type of delivery.

TABLE III

TYPE DELIVERY	GROUP I	GROUP II	TOTAL
Spontaneous delivery	45—51.1%	110—51.6%	155—51.4%
Operative delivery	43—48.9%	103—48.4%	146—48.6%
Low forceps	41	96	
Episiotomy	42	97	
Breech extraction	2	5	
Midforceps	0	2	

Medication

As previously mentioned, various forms of medication were used in Group I; therefore, no mention will be made in this article regarding specific medication used in the group other than whether or not scopolamine was used. The percentage of patients receiving scopolamine is shown in Table V.

TABLE IV

TYPE CASE	MINIMUM AMT. USED	MAXIMUM AMT. USED	AVERAGE
Primiparas (FT)	300 mg. (5 gr.)	720 mg. (12 gr.)	360 mg. (6 gr.)
Multiparas (FT)	150 mg. (2½ gr.)	600 mg. (10 gr.)	300 mg. (5 gr.)
Primiparas (PM)	180 mg. (3 gr.)	480 mg. (8 gr.)	300 mg. (5 gr.)
Multiparas (PM)	300 mg. (5 gr.)	480 mg. (8 gr.)	330 mg. (5½ gr.)

All of the patients in Group II received vinbarbital sodium intravenously and some received a supplemental oral dose. The minimum intravenous dose used was 150 mg. (2½ grains) and the maximum total dosage given to any one

patient was 720 mg. (12 grains). Table IV summarizes the average, minimum, and maximum amounts used for primiparas and multiparas, both full-term (FT) and premature (PM) labors.

Patients were given an initial dose of 300 mg. (5 grains) vinbarbital sodium intravenously as soon as labor was definitely established, followed immediately by $\frac{1}{130}$ grain of scopolamine. Additional doses of from 120 mg. (2 grains) to 180 mg. (3 grains) vinbarbital sodium were administered at one- to five-hour intervals as required to maintain an effective degree of analgesia. In about 5 per cent of the cases an additional dose of $\frac{1}{200}$ grain of scopolamine was given after six hours. An attempt was made to avoid giving any scopolamine within an hour before delivery. In several instances vinbarbital sodium was given as close as twenty minutes prior to delivery with no apparent ill effects. In the event a patient entered the hospital late in labor smaller initial doses of vinbarbital sodium were used and many times no scopolamine was given.

TABLE V. SUMMARY OF CASES

	GROUP I.				GROUP II.				NO MEDICATION	
	FULL TERM		PREMATURE		FULL TERM		PREMATURE		FULL TERM	
	PRIM.	MULT.	PRIM.	MULT.	PRIM.	MULT.	PRIM.	MULT.	PRIM.	MULT.
No. cases	35	40	7	6	93	107	7	6	2	12
Average age	22	26	21	26	21	27	25	28	28	30
Labor*										
1st Stage	650	490	330	301	402	242	274	218	235	190
2nd Stage	70	31	59	34	45	28	34	13	96	31
3rd Stage	4	6	4	5	4	4	5	4	3	6
M—2†	316	208	135	130	164	78	105	104	-	-
Amnesia (%)										
0	***	***	***	***	2%	3%	14%	0	-	-
+	***	***	***	***	21%	17%	14%	33%	-	-
++	***	***	***	***	77%	80%	72%	66%	-	-
Depression of babies										
0	23	30	0	2	88	101	5	5	2	12
	(66%)	(75%)	0	(33%)	(95%)	(95%)	(72%)	(83%)	(100%)	(100%)
+	10	4	3	2	3	3	1	0	0	0
	(28%)	(10%)	(43%)	(33%)	(3%)	(3%)	(14%)	0	0	0
++	2	6	0	0	2	2	0	1	0	0
	(6%)	(15%)	0	0	(2%)	(2%)	0	(17%)	0	0

*Stages of Labor indicated in minutes.
***Data not obtained.
†Number of minutes between first medication and complete dilatation.

A preliminary oral dose of vinbarbital sodium of from 0.2 to 0.3 Gm. (3 to 4½ grains) was used in nine patients. These were primiparas who entered the hospital in the early stages of labor and were extremely apprehensive. In no case did this retard the establishment of active labor. As soon as the cervix showed 4 cm. dilatation in these cases, the full dose of vinbarbital sodium and scopolamine was given. One patient in the series received a total of 0.2 Gm. (3 grains) orally and 720 mg. (12 grains) intravenously of vinbarbital and $\frac{1}{130}$ grain scopolamine with no apparent ill effects to either the mother or the infant.

Duration of Labor

An attempt was made in this study to compare the duration of labor of patients receiving vinbarbital sodium with those receiving other forms of medication and those receiving no medication of any kind. This comparison is shown in Table V. Since any statistics for the first stage of labor are unavoidably inaccurate due to the fact the time of onset of labor is usually ob-

tained from the patient, an effort was made to provide a more accurate interval for comparison. Table V contains a column showing the interval of time elapsing between the time the first medication was given and the beginning of the second stage. This is identified as M-2. In this table cases were analyzed according to parity and according to whether the patient was at term or in premature labor.

From this it can be seen that while in primiparas the difference in the second stage between Group I and Group II amounted to only 25 minutes, the average of M-2 was 152 minutes less for Group II. Similar statistics appear for multiparas with Group II averaging 130 minutes less than for Group I. For premature labors the difference varied from 26 to 30 minutes. The over-all average for all cases shows that Group II cases reached complete dilatation 111 minutes earlier from the time of the first medication than did Group I cases.

The first stage averaged 138 minutes less for Group II. The third stage averaged the same for both groups. These statistics compare rather favorably with the group of patients receiving no medication with the exception of the first stage. This can no doubt be explained by the paucity of cases in the latter group.

Effects on the Mother

There were no apparent untoward effects on the mothers in the Group II cases. There were two cases of postpartum hemorrhage in the entire series. One of these occurred in Group II in a patient with a retained placenta requiring manual removal. The other occurred in a primipara in the group receiving no medication. This was an atonic hemorrhage with no apparent explanation.

This drug has the definite advantage of permitting the patient to cooperate while in labor. There was very little excitation among this group of patients. Those patients receiving no scopolamine showed none at all. Patients receiving an initial oral dose of vinbarbital sodium showed no excitation even though they had received scopolamine.

There were no cases of respiratory embarrassment. One patient entered the hospital in active labor shortly after eating a large meal and vomited during the last few minutes of the second stage when open-drop ether was administered. There was some aspiration of the vomitus, and the anesthesia was stopped immediately. The patient coughed up the aspirated material. She was delivered and the episiotomy repaired with no additional anesthesia. Her postpartum course was afebrile.

Amnesia was evaluated by asking patients afterwards regarding their ability to recall events during their labor. Many patients had total amnesia from ten minutes after the medication was given. The amount of amnesia was graded as follows: 0, little or no amnesia; +, moderate amnesia; ++, total amnesia. Some patients had total amnesia for the period of time they were in the labor room but apparently had a lucid period while being taken to the delivery room; these were included in the group obtaining a moderate amount of amnesia. The over-all average showed 5 per cent of all patients having little or no amnesia; 21 per cent having a moderate amount; and 74 per cent with total amnesia. It was observed that although some patients did not seem to be receiving adequate effects, very few remembered any part of their labor.

Most patients reacted within two hours after delivery, the average being 125 minutes. No patients complained of drowsiness or headache after reacting. There was no nausea.

Effects on Infants

From the 301 mothers there were delivered 303 babies (two sets of twins). Of these 302 were born alive; there was one stillborn fetus with congenital syphilis. Table VI shows a summary of stillbirth and neonatal mortality.

TABLE VI. STILLBIRTH AND NEONATAL MORTALITY

	GROUP I	GROUP II
Full-term pregnancies	75	200
Stillborn	0	1
Neonatal deaths:		
Atelectasis*	1	0
Erythroblastosis fetalis	1	0
Premature labors:	13	13
Neonatal deaths:		
Atelectasis* (both viable)	1	1
Multiple congenital deformities (6 months)	1	0
Total infants lost:		
Gross mortality	4 (4.5%)	2 (.9%)
Corrected mortality	3 (3.4%)	1 (.4%)

*Infants showed definite atelectasis and no other abnormality.

In an effort to evaluate the degree of asphyxia in infants they were classified into three groups: 0, cried spontaneously and required no form of resuscitation; +, cry slightly delayed and required only clearing of air passages; ++, cry delayed and oxygen and other forms of resuscitation required in addition to clearing the air passages. From Table V it can be seen that 63 per cent of the infants in Group I cried spontaneously, whereas 94 per cent in Group II fell into this classification. In Group I, 21 per cent showed mild asphyxia, and only 3 per cent in Group II. Severe asphyxia was seen in 6 per cent of the infants in Group I and in 2 per cent of the infants in Group II.

Complications Directly Attributable to the Drug

In the entire series of 213 cases in Group II there was only one instance in which it was felt that complication could be attributed to vinbarbital sodium. One patient showed a marked induration and a moderate degree of inflammation in the antecubital space at the site of injection. This was attributed to extravasation of the drug into the surrounding tissues. A small needle was used because the patient had very small veins, and it is believed that the vein may have been punctured on the wall opposite the site of injection. It is the opinion of the author and of others who have used vinbarbital sodium that a No. 20 or 21 needle should be used to obviate any danger of either puncturing the vein or failing actually to enter the lumen of the vein, thus resulting in extravasation of the solution.

Summary of Results

A series of 213 unselected cases (Group II) of term and premature pregnancies receiving vinbarbital sodium as an analgesic agent were compared with 88 cases (Group I) of term and premature pregnancies receiving other forms of obstetric analgesia. The range of ages varied from 15 to 45 years.

Approximately 51 per cent of each group were delivered spontaneously. In Group I, of the 43 cases having an operative delivery, 41 were delivered by low forceps, 2 by breech extraction; and in Group II, of the 103 cases having an operative delivery, 96 were delivered by low forceps, 5 by breech extraction, and 2 by midforceps.

Patients received an average dose of 5 grains of vinbarbital sodium intravenously. Some patients were given a combination of oral and intravenous medication. The maximum dose given was 12 grains. Scopolamine was given in a dosage of $\frac{1}{130}$ grain and repeated once if necessary in the dosage of $\frac{1}{200}$ grain.

A comparison of the length of labor between Groups I and II was made. This showed that the first stage averaged 138 minutes less for Group II cases; 25 minutes less in the second stage; and no difference in the third stage. Further comparison of the interval between the time the first medication was given and the beginning of the second stage revealed that Group II cases reached the second stage on an average of 111 minutes earlier.

In evaluating the amount of amnesia obtained from vinbarbital sodium it was shown that 5 per cent showed little or no amnesia; 21 per cent showed a moderate amount of amnesia; and 74 per cent showed total amnesia.

In Group I, of 88 babies delivered, there were 4 deaths. Of these, one was a nonviable premature with multiple congenital deformities resulting in a corrected infant mortality rate of 3.4 per cent. In Group II, of 213 babies delivered, there was one death and one stillborn fetus, resulting in a corrected infant mortality of 0.4 per cent.

Of the children born alive, 63 per cent in Group I cried spontaneously while 94 per cent in Group II cried spontaneously; 21 per cent showed mild asphyxia in Group I and 3 per cent in Group II; 6 per cent of the infants in Group I showed severe asphyxia and 2 per cent of Group II fell into this classification.

Induration and inflammation at the site of injection occurred in one patient. This was the only complication directly attributable to vinbarbital sodium.

Conclusions

1. It was found that Delvinal vinbarbital sodium was a safe and satisfactory drug providing analgesia and amnesia during labor.

2. It was found that this drug can be given orally or intravenously or in a combination of both with safety to both the mother and baby. Doses totaling as much as 12 grains may be used. Most patients can be carried through labor of average length with 5 grains. Scopolamine may be used as an adjunct in providing additional amnesia.

3. Labor is shortened by the use of Delvinal vinbarbital sodium.

4. Infants show very little respiratory difficulty when this drug is used as an obstetric agent.

5. Patients obtain good amnesia and analgesia and are cooperative, and they react from anesthesia without any depressive effect.

6. It is recommended that a No. 20 or 21 needle be used to administer the drug intravenously in order to prevent extravasation of the material.

References

1. Bernstine, J. B., and Prince, L. L.: Am. J. Obst. & Gynec. **45**: 851, 1943.
2. Burkons, H. F.: Am. J. Obst. & Gynec. **56**: 549, 1948.
3. Carmichael, E. B., and Thompson, W. D.: Proc. Soc. Exper. Biol. & Med. **46**: 233, 1941.
4. Evans, J. R.: Am. J. Obst. & Gynec. **47**: 821, 1944.
5. Fournier, L. G.: Am. J. Obst. & Gynec. **56**: 913, 1948.
6. Hendrix, J. P.: Am. J. M. Sc. **204**: 93, 1942.
7. Kohl, M. F. F.: Am. J. Obst. & Gynec. **56**: 811, 1948.
8. Lewis, M. S.: Am. J. Obst. & Gynec. **51**: 395, 1946.
9. Lewis, M. S., and Boddie, J. B., Jr.: South. M. J. **41**: 820, 1948.

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GONADOTROPIN IN SPINAL FLUID IN A CASE OF TWIN PREGNANCY

Criticism of Spinal Fluid Test for Diagnosis of Hydatidiform Mole

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TO DETERMINE if a hydatidiform mole has developed during the course of a pregnancy may be a very difficult problem in differential diagnosis. The demonstration of an increased excretion of gonadotropic hormone can be helpful, but it has been pointed out repeatedly that many women during the first trimester of pregnancy may have peaks of gonadotropin excretion which exceed the titers frequently found in cases of mole.[8, 11, 14] In standard textbooks,[3, 10] one finds it stated that the demonstration of gonadotropic hormone in the spinal fluid is diagnostic either of hydatidiform mole or chorionepithelioma. This dictum is based probably on Zondek's statement[19] that prolan B is never found in the spinal fluid during the course of a normal pregnancy. H. M. Evans[5] had earlier made a similar statement. A number of papers have appeared[4, 7, 9, 16, 17, 18] reporting short series of cases in which examination of spinal fluid for gonadotropin, either by the Aschheim-Zondek or Friedman methods, was helpful in the diagnosis of hydatidiform mole. All of these papers include deplorably small numbers of control cases of normal pregnancies, particularly during the period of the usual peak in hormone excretion.

In a recent case from the private practice of one of us (E. A. H.), in which the possibility of the development of a mole was suspected for clinical reasons, hormonal studies of urine and spinal fluid were dangerously misleading. For this reason, a survey of the literature was undertaken to ascertain the basis for the oft-quoted statement that the demonstration of gonadotropin in spinal fluid is diagnostic of the presence of hydatidiform mole or chorionepithelioma.

We were surprised to learn that published work indicating that pregnancy hormone appears in the spinal fluid in cases without either mole or chorionepithelioma had been either overlooked or ignored. In 1930, Aronowitsch[1] reported the results of Aschheim-Zondek tests on the spinal fluids of twenty-eight pregnant women, and in three of these a positive reaction (R III) was obtained. Shortly thereafter, Aschheim[2] quoted Califanza as having obtained a luteinizing reaction in mice with 3 c.c. of cerebrospinal fluid from three of twenty-eight pregnant women. In 1932, Hashimoto[12] reported five positive A-Z reactions in normal pregnancies, but he used as much as 18 to 20 c.c. of spinal fluid. In five cases of mole, positive tests required 12 to 16 c.c., and in one case of chorionepithelioma, 16 c.c. In a case of eclampsia, a positive reaction was obtained with 12.4 c.c. of spinal fluid. Hashimoto claimed that, in the absence of eclampsia, a positive reaction with less than 16 c.c. of spinal fluid was proof of hydatid mole or chorionepithelioma. The difference between 16 c.c. and 18 c.c., the amount which gave a positive reaction in normal pregnancy, appears danger-

ously small. The same year, Kulka[13] examined the spinal fluids of twenty-five pregnant women, including seven cases of eclampsia. All were negative for prolan. But in five women who were in the second and third lunar months of their pregnancies, and who had hyperemesis gravidarum, three gave positive tests with their spinal fluids. Schulze,[15] in 1942, briefly told of unpublished work of Palmer who tested the spinal fluids of forty-two supposedly normal pregnant women, and in six of these obtained positive tests for gonadotropic hormone. Three of these tests were done by the Aschheim-Zondek method, using 2 c.c. of spinal fluid for each animal; and three by the Friedman method, using 5, 13, and 15 c.c. of spinal fluid in each rabbit, respectively.

Although it appears clear that, in some cases of hydatid mole and chorion-epithelioma, chorionic gonadotropin can be found in the cerebrospinal fluid, positive tests are also obtained in some cases of normal pregnancy. It may well be that the presence of the hormone in spinal fluid is related to the blood level; above a certain titer in the blood, it may spill across the blood-cerebrospinal fluid barrier. This has been discussed briefly by Garcia and his co-workers.[9] Surprisingly, correlated studies of blood and spinal fluid titers have not been reported. If such a relationship be found, then it might be expected that at peaks of gonadotropin output, as reported by Evans, Kohls, and Wonder,[6] appreciable amounts would pass into the spinal fluid. It is known that the urinary excretion of prolan may be high not only at the sixth to eighth weeks of pregnancy, but also in cases with toxemia, and in cases of multiple pregnancy.

The following case report illustrates the difficulties of differential diagnosis, and the fallacy of relying upon the demonstration of gonadotropin in the spinal fluid as an absolute criterion of the development of a mole.

Case Report

Mrs. R. D., aged 26 years, was first admitted to Beth Israel Hospital on Sept. 19, 1948, because of vaginal bleeding. She had last menstruated on June 22. One month later, nausea had begun, becoming increasingly severe, persisting, and accompanied by vomiting. Sedation and pyridoxine were somewhat helpful.

The patient had had one previous pregnancy, in 1946, which had terminated in the third month, by spontaneous abortion. Following that, a curettage was performed. For retroflexion, a suspension was performed in June, 1947.

Sept. 19, 1949, approximately thirteen weeks from the onset of her last menstrual period, she noticed a stream of thick, dark blood issuing from the vagina. To her knowledge, no clots or tissue were passed. She felt no cramps. On admission to the hospital that day, the uterine fundus was felt one fingerbreadth above the umbilicus (nine days before, it had been felt midway between pubis and umbilicus); the uterus felt broad and tense, but not tender or indurated The vaginal bleeding was not profuse; no tissue, clots, nor vesicles were found.

Pulse and temperature were normal. Blood pressure was 94/60. The red blood cell count was 3,370,000 with 9.5 Gm. of hemoglobin; the white blood cell count was 9,500. The urine was normal. Severe nausea was present, and the patient had been having headaches for two weeks.

Because of the rapid increase in the size of uterus, vaginal bleeding, unusually severe nausea, vomiting, headache, and anemia, the diagnoses of hydatid mole, and of multiple pregnancy with polyhydramnios were considered. Careful examination of the vaginal discharge revealed no vesicles. X-ray examination of the abdomen on October 2 revealed no evidence of a fetus. Friedman test, performed with 5 c.c. of urine diluted one to eighty, was positive.

The bloody vaginal discharge ceased twelve days after admission. Four days later, on October 6, she was discharged from the hospital, feeling better. It was decided to watch the patient carefully.

On October 23, the patient was readmitted to the hospital because of recurrence of nausea, vomiting, and weakness. The fundus of the uterus was now three fingerbreadths above the umbilicus. Because the suspicion of hydatid mole was now stronger, urine was sent to the laboratory for quantitative assay of gonadotropin and spinal fluid was withdrawn to determine if it contained gonadotropic substance (because of the statements in the literature that the demonstration of gonadotropin in spinal fluid was evidence of hydatid mole or chorionepithelioma). On the day these tests were completed, another x-ray of the abdomen was taken, and this time definite evidence of twin pregnancy was seen. It was found, however, that 5 c.c. of spinal fluid gave a positive Friedman test; and 5 c.c. of one to eighty dilution of urine was also positive.* It was felt that the twin pregnancy explained the clinical course and laboratory findings. The patient was discharged.

On Feb. 2, 1949, she was again admitted to the hospital because of difficulty in breathing, nausea, and vomiting. The uterus, with its twin pregnancy, was very large. Dilated intestinal loops were felt in the upper abdomen; x-ray examination, however, gave no evidence of intestinal obstruction. Two days later, seven and one-half weeks before term, she went into labor. After a seven-hour labor, she was delivered of twins. The first was a macerated fetus, the second a living infant weighing 4¼ pounds. The placenta was removed manually. Careful examination revealed no evidence of mole. A transfusion of 500 c.c. was given. The patient made an uneventful convalescence and was discharged from the hospital on the ninth postpartum day.

Unfortunately, the infant, born alive, developed hemorrhagic disease, and died on the fifth day. No autopsy was performed. Although the mother was Rh negative and the father Rh positive, there was no evidence of antibody formation.

Five weeks post partum, the patient was admitted to another hospital because of massive vaginal bleeding. In attempts at controlling the hemorrhage, the uterus was perforated, and a hysterectomy was performed. Through the courtesy of the pathologist, we were able to examine the uterus. It showed retained placental tissue and some low-grade inflammation. There was no evidence of hydatidiform change in the number of sections examined. A small cyst received with the uterus proved to be peritoneal.

The patient's subsequent course has been uneventful.

Discussion

The differential diagnosis of mole is frequently difficult. When the quantitative titration of urine for gonadotropin was first introduced, it was felt that there was had a diagnostic tool with which the problem could be solved. It was soon learned that such determinations must be interpreted with the greatest of caution. To quote Schulze,[15] "The interruption of a number of cases of normal twin pregnancy, and one triplet pregnancy, whose too rapid enlargement of the uterus plus high hormone values had led to a diagnosis of mole, showed that the matter was not so simple."

It would indeed be almost providential if the demonstration of gonadotropin in spinal fluid were diagnostic of mole or chorionepithelioma. Unfortunately, as the survey of the literature indicates, it is not. The case reported is somewhat complicated. In addition to the twin pregnancy, it is probable that there was some degree of toxemia. It is, however, in just such cases that the problems of differential diagnosis arise. Had not the x-ray plate taken on October 23 shown incontrovertible evidence of twins, there would have been strong temptation to interrupt the pregnancy. (In the light of the unfortunate subsequent course of events, this might have saved much heartache for both patient and doctor.) It is clear, however, that a positive test for gonadotropin in spinal fluid may occur in pregnancies uncomplicated by hydatidiform mole or chorionepithelioma.

*Quantitative A-Z, done several days later at the Women's Clinic, New York Hospital, through the courtesy of Dr. Charles T. Snyder, was reported negative at 1:80 dilution.

Summary

1. A case of twin pregnancy is presented in which the spinal fluid contained gonadotropic hormone.

2. The literature is surveyed, and no basis is found for the contention that the demonstration of gonadotropic hormone in the spinal fluid is diagnostic of hydatid mole or chorionepithelioma.

References

1. Aronowitsch, G. D.: Endokrinologie **7**: 113, 1930.
2. Aschheim, S.: Arch. f. Gynäk. **144**: 165, 1930.
3. Crossen, H. S., and Crossen, R. J.: Diseases of Women, ed. 9, St. Louis, 1944, The C. V. Mosby Company.
4. Ehrhardt, K.: Arch. f. Gynäk. **148**: 235, 1932.
5. Evans, H. M.: J.A.M.A. **104**: 464, 1935.
6. Evans, H. M., Kohls, C. L., and Wonder, D. H.: J.A.M.A. **108**: 287, 1937.
7. Ewald, F. K.: Zentralbl. f. Gynäk. **60**: 559, 1936.
8. Frank, R. T.: J. Mt. Sinai Hosp. **10**: 112, 1943.
9. Garcia-Huidobro, M., and Paredes, L.: Bol. Soc. chilena de obst. y ginec. **11**: 31, 1946.
10. Greenhill, J. P.: Obstetrics in General Practice, ed. 2, Chicago, 1941, The Year Book Publishers.
11. Hamburger, C.: Acta obst. et gynec. Scandinav. **24**: 45, 1943.
12. Hashimoto, H.: Zentralbl. f. Gynäk. **56**: 2247, 1932.
13. Kulka, E.: Zentralbl. f. Gynäk. **56**: 2774, 1932.
14. Schoeneck, F. J.: Am. J. Obst. & Gynec. **39**: 485, 1940.
15. Schulze, M.: Clinics **1**: 685, 1942.
16. Vesell, M., and Goldman, S.: Am. J. Obst. & Gynec. **42**: 272, 1941.
17. Vilegzhanin, A. I.: Akush. gin. No. 11: 5, 1940.
18. Yaber, M.: Rev. obst. y ginec., Caracas **5**: 175, 1945.
19. Zondek, B.: J. Obst. & Gynaec., Brit. Emp. **49**: 397, 1942.

Zondek, Bernhard, and Rozin, Samuel: Stimulation of Ovarian Function and Induction of Pregnancy Through Intravaginal Implantation of Estrogen Pellets, Surg., Gynec. & Obst. **88**: 783, 1949.

The authors have treated 62 women for amenorrhea by intravaginal implantation of pellets consisting of either estradiol, or in most cases, estrone. Seven of the patients suffered from primary amenorrhea, and fifty-five of them had secondary amenorrhea of two to ten years' duration. All had an unfavorable prognosis. Fifty-two women responded with bleeding, and thirty-eight reported several cyclic periods. Twenty-six had regular periods for up to twelve months, and in twelve the cycle was completely established; eight of the latter women became pregnant.

The authors have apparently determined that the intravaginal implantation of pellets possesses the following advantages over subcutaneous administration: (1) The effect is more constant since there is less connective tissue; (2) The effect is five times more intense; and (3) The tablets are seldom expelled.

The average interval between implantation and onset of the bleeding was seventy-eight days.

The dosage varied according to the clinical symptoms, but in no instance should it exceed 50 mg. as unwelcome symptoms of menorrhagia might appear. Louis M. Hellman.

CYCLIC CHANGES IN VAGINAL POPULATIONS OF EXPERIMENTALLY INDUCED TRICHOMONAS VAGINALIS INFECTIONS IN RHESUS MONKEYS

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IT IS generally observed by clinicians that exacerbations of human vaginal trichomoniasis occur around the time of menstruation and that symptoms are usually more severe during this interval. However, detailed studies on the trend of parasite population in individual patients seem not to have been reported. Such facts, if available, could be of importance in diagnosis and in assessing the efficacy of a therapeutic regimen. It is the purpose of the present study to report observations on the course of the infection in monkeys, with the hope that similar studies on strictly isolated human patients may be forthcoming.

Method

A colony of rhesus monkeys was maintained in separate cages to prevent cross-infection. The cages were scrubbed and steam-sterilized each week. None of the monkeys in the colony was found to harbor a natural infection of trichomonads. One milliliter of a recently isolated strain of bacteria-free *Trichomonas vaginalis*[1, 2] from a forty-hour culture, maintained in an STS medium,[3] was introduced into the vagina by means of a tuberculin syringe. Subsequent examinations for the presence of parasites were made by introducing a cotton applicator between the blades of a nasal speculum which was used to part the labia. The specula were kept in boiling water between examinations of successive animals to prevent cross infection. The applicators were placed in tubes containing a standard 1 ml. of modified Ringer's solution and the adherent vaginal discharge was dispersed. These specimens were kept at room temperature until it was convenient to examine them. Maintenance at this reduced temperature did not interfere with the motility and detection of the protozoa, since positive findings were readily made as much as two hours after collection of the material. Microscopic examination was made by the hanging-drop technique and the number of trichomonads was determined per low-power field. Although the accuracy of this technique is admittedly low, the day-to-day variation in numbers of observed trichomonads as recorded below was great enough to make the data on cyclic changes in populations significant. The examinations were made three times per week. Careful records were kept of the menstrual cycles of each animal, and in addition, each animal was regularly palpated[4] to establish the state of the uterus and the time of ovulation. Smears were prepared and stained for glycogen content, using iodine-potassium iodide according to the Mack technique.[5] One series of animals was examined carefully by means of an endoscope for signs of inflammation of the vaginal and cervical mucosa.

Results

In no case did any of the infected monkeys develop signs of vaginitis. No "strawberry spots" were observed on the mucosa. The cervices appeared normal and there was no appreciable difference in the amount or character of the vaginal discharge from infected and noninfected monkeys.

The elapsed period between inoculation and first demonstration of successful implantation of trichomonads varied from two to twenty-three days. The duration of the infection varied from fifty-one to four hundred seventy-nine days, with several of the latter monkeys still maintaining their initial infection at the time of this report. While self-limitation of this infection does occur, it is apparently not the usual course. (This observation is in contrast to the findings of Trussell and McNutt,[6] who followed a smaller series of animals.) Although our experience with juvenile monkeys has been limited to three animals, it would seem that young animals are refractory to infection with *T. vaginalis* and that success in implanting the trichomonads is not likely until after the onset of the first menses.

The most striking feature observed in these experimentally induced infections was the abruptness of the fluctuations in the number of trichomonads. During the midcycle the populations tended to subside to the point where either the parasites could not be found or the numbers were restricted to 1 or 2 organisms per microscopic field. The duration of these periods of very low population varied from nine to thirty-seven days. In the period just before and just after the menstrual flow, sudden increases in population occurred. In a period of forty-eight hours the population in many instances was observed to change from a condition in which none or very few trichomonads could be found to one in which too many were present to permit an accurate count. These periods of high population generally persisted for but a few days. It was usual for two peaks to be reached in each cycle, one just after the period and another just before the onset of the next flow. These facts are illustrated in the curves shown in Fig. 1, A to E.

In Fig. 1, F, which is a composite of the findings on numerous animals, the number of times that a population peak was reached on a given day of the cycle is plotted in reference to the time of menstruation. Here it may be seen that the population peaks for different individuals, while centering around the time of the menstrual flow, may occur as early as twelve days before and as late as seven days after the period, although in the majority of instances peaks were reached in the interval of three days prior to and five days following the menses.

To date no satisfactory explanation of this periodicity in population change has been forthcoming. There was no correlation of abundance of trichomonads with the amount of glycogen in the stained vaginal smears, nor with the time of ovulation. One observation was consistently made which relates to the presence or absence of leucocytes in the vaginal fluid. In the absence of demonstrable leucocytes no trichomonads could be found. However, the correlation here does not appear to be quantitative, since high populations of parasites were frequently associated with moderate to low numbers of white cells. Further studies are in progress in a search for specific causal factors related to these periodic changes in parasite population.

One interesting case was observed in Monkey No. 11 during the months of January and February, 1947. This animal bled twice during January with an intervening period of only six days. As may be seen from Fig. 1, C, she subsequently maintained a very high population for twenty-two consecutive days. Whether or not this bears any relationship to the impact of the two

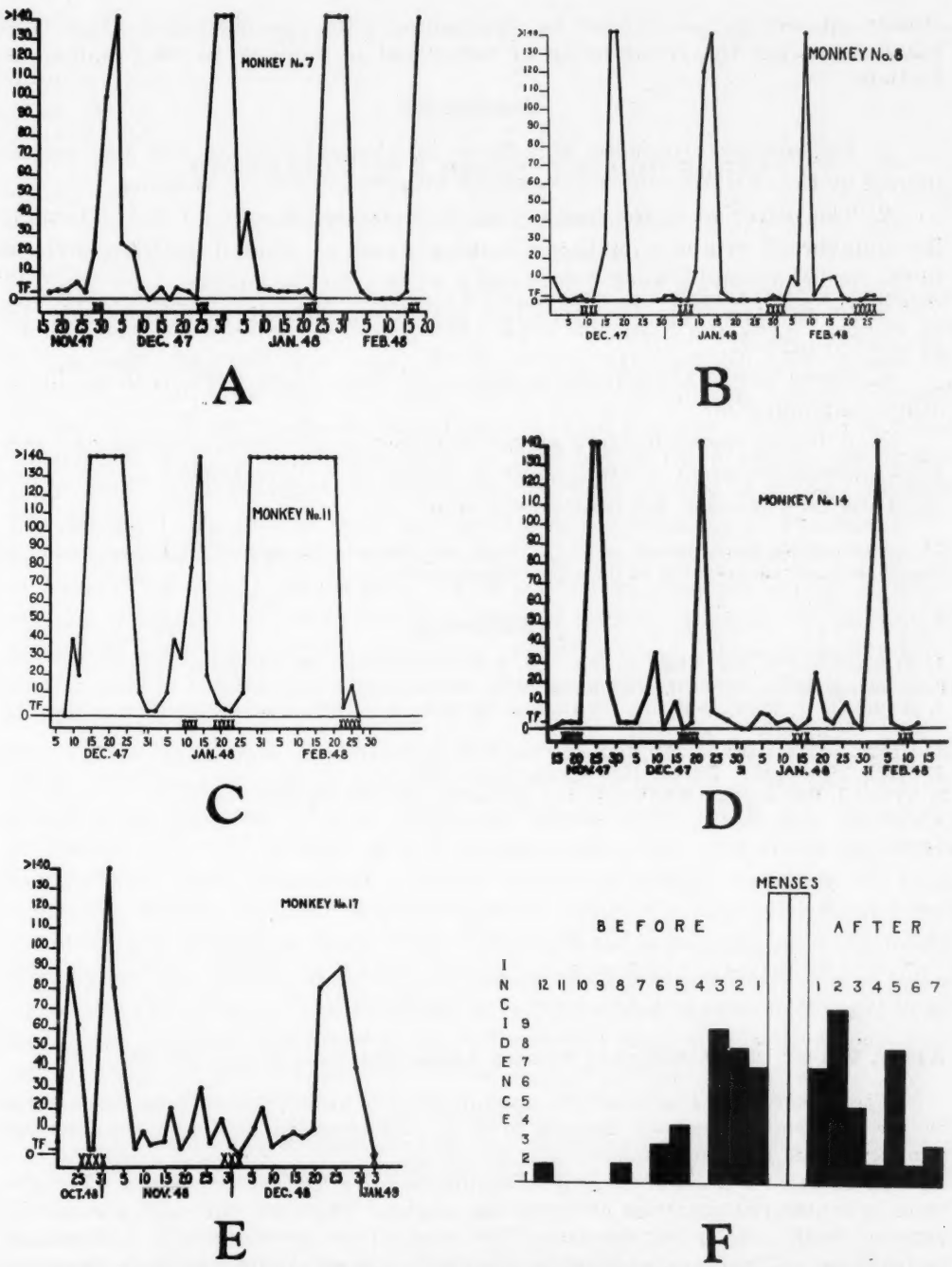

Fig. 1.—A to E, Fluctuations in vaginal trichomonad populations in five different monkeys. The number of trichomonads per low-power field is shown on the vertical axis. TF = less than one trichomonad per low-power field. X = days on which menstrual bleeding was observed. In C, the first menstrual period, December 1 to 4, is not shown. Attention is called to the abnormally short cycle in mid January, 1948, followed by a prolonged elevation in parasite population. This was the only observed case of this kind.

F, Summary of observed population maxima in nineteen infected monkeys. The number of times that a peak in population was reached is plotted on the vertical axis. The days before or after the menses on which such peaks were reached are plotted on the horizontal axis. It is clear that such maxima are reached most frequently in the period around menstruation. On the other hand, it is shown that in all infected monkeys population maxima were reached only twice on the twelfth day and twice on the eighth day prior to menstruation.

closely spaced menses cannot be determined until specific information is at hand regarding the relationship of menstrual physiology to trichomonas infections.

Conclusions

1. *Trichomonas vaginalis* infections in rhesus monkeys are not accompanied by the objective signs of vaginitis observed in human patients.

2. The infection in the monkey is characterized by abrupt fluctuations in the number of protozoa, with peak populations of brief duration restricted to the period around a week before and a week after the menses.

3. In the midcycle the parasites are often difficult to demonstrate for prolonged periods.

4. There are at present no experimental data which explain these fluctuations in population.

5. A better understanding of the infection in the human female and perhaps greater accuracy of judgment in diagnosis and treatment might result from similar studies of the infection in man.

The authors are indebted to Mr. P. Russo for his able assistance in the management of the animals and maintenance of the experimental series.

References

1. Trussell, Ray E., and Plass, E. D.: Am. J. Obst. & Gynec. **40**: 883, 1940.
2. Johnson, Garth, Trussell, M., and Jahn, F.: Science **102**: 126, 1945.
3. Kupferberg, A. B., Johnson, Garth, and Sprince, H.: Proc. Soc. Exper. Biol. & Med. **67**: 304, 1948.
4. Hartman, Carl G.: Contrib. Embryol., Carnegie Institution of Washington **13**: 1, 1932.
5. Mack, Harold C.: Harper Hosp. Bull. **1**: 54, 1942.
6. Trussell, Ray E., and McNutt, S. H.: J. Infect. Dis. **69**: 18, 1941.

Kaeser, Von O.: The Aetiology of Primary Amenorrhea, Gynaecologia **127**: 220, 1949.

The author reports in detail ten cases of primary amenorrhea with emphasis placed on the differential diagnostic features of each. He recognizes two main classifications: pituitary failure and ovarian failure.

In his own ten cases, five were probably pituitary in origin and two ovarian. The other three presented malformations of uterus and vagina. There are two cases presented in extensive detail pointing out the classic differences between primary ovarian and pituitary amenorrheas. Although no endometrial biopsies or vaginal smears were done, the author did complete hormone determinations and extensive x-ray studies of the long bones and skull. The most striking changes were noted in the skull (small frontal sinuses, and small sella in pituitary dysfunction) and in the long bones of the hand which revealed retarded ossification in the pituitary group. The general body types of these cases conformed to the x-ray findings. The differences in hormone findings, sugar tolerance tests, basal metabolism rate, etc., were not conclusive enough to warrant in themselves a diagnosis of either pituitary or ovarian failure.

Treatment (if the diagnosis can be made) is obviously replacement therapy.

Eugene N. Scadron.

OPERATION OF A GROUP O BLOOD BANK*

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THE chief difficulty in maintaining a blood bank in a small hospital is keeping an adequate supply of fresh blood. Type specific transfusions require the use of eight different blood types, O, A, B, and AB, both Rh positive and Rh negative. If all these types are not stocked, the purpose of the bank is defeated in that blood is not available immediately. If all types are stocked there is a tremendous waste because blood must be used within three weeks. Small hospitals have too few transfusions to keep the blood moving at a constant rate. One answer to the problem is in the use of group O blood for all patients.

A group O blood bank is very simple. Only two types of blood are required, O Rh-positive and O Rh-negative. This ensures an adequate supply of blood without the danger of waste during periods of lessened demand. Opposition to the use of group O blood for patients of the other blood groups is largely theoretical and is usually voiced by those who have not used it. Published data stress the relative freedom from reactions.

The technical factors involved in the use of group O blood are not complex. Group O blood contains no agglutinogens but does contain alpha and beta agglutinins as shown in Table I. These agglutinins in the serum may clump the red blood cells which contain A or B agglutinogen if the titer of the agglutinin is sufficiently high. The donor's blood is usually sufficiently diluted by the large volume of circulating blood of the recipient to reduce the titer of alpha and beta agglutinins to a harmless level. This was considered satisfactory until Witebsky brought out his specific A and B substance which will neutralize the α and β agglutinins in vitro. A and B substance may be added to each bottle of O blood or, if it is preferred, high titer (1:32 or higher) O blood may be given only to O patients and low titer O blood reserved for A, B, and AB patients.

TABLE I

BLOOD GROUP	AGGLUTINOGENS	AGGLUTININS
O	—	$\alpha\beta$
A	A	β
B	B	α
AB	AB	—

No cross-matching is necessary and is even misleading because the minor cross, patient's cells and donor's serum, will usually show clumping. Because of this, a safety factor is necessary to be doubly sure the donor's blood is group O. This may be done by typing the serum with A and B cell suspensions (Table II) or by cross-matching with a "known O" blood.

*Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, Nov. 8, 1948.

In some sections of the country, the use of nonspecific group O blood for transfusion is feared. That this fear is largely theoretical and without practical basis, makes it none the less real. The author had used nonspecific group O blood to transfuse patients of all types in civilian practice and in the Army during the recent war. Both of these experiences showed that no more reactions were encountered than with the use of type specific transfusions.

Accordingly we established a group O blood bank at Pittsburgh Hospital on April 4, 1947. This is a general hospital of 225 beds. We had an average of seven to ten transfusions per month before establishment of the bank. This has risen to an average of 25.6 per month over the eighteen and one-half months of the bank's operation. The load varies but we find that a supply of 10 pints of type O Rh-positive blood and 2 to 4 pints of type O Rh-negative blood is an adequate amount to keep in the bank. Blood is preserved in A C D solution (citric acid, sodium citrate, and dextrose) and is used up to 21 days after withdrawal. Occasionally a family will have trouble finding type O donors, especially if repeated transfusions are necessary. We have no quarrel with the use of type specific blood under such circumstances. Some of our physicians prefer to use type specific blood and we honor this desire if it does not complicate our routine. One of the virtues of a blood bank is that it simplifies the work of the laboratory and permits this work to be done at leisure after the transfusion and during the normal working hours of daylight. Most blood banks do not hesitate to use type O blood when they cannot obtain the rare types and yet they hesitate to use it routinely.

TABLE II. TYPING "O" BLOOD

A serum (β agglutinin) plus O erythrocytes	= no agglutination
B serum (α agglutinin) plus O erythrocytes	= no agglutination
O serum ($\alpha\beta$ agglutinins) plus A erythrocytes	= agglutination
O serum ($\alpha\beta$ agglutinins) plus B erythrocytes	= agglutination

TABLE III. BLOOD TRANSFUSIONS, PITTSBURGH HOSPITAL

DONOR	RECIPIENT	TOTAL	REACTIONS*	PER CENT REACTIONS		
O	A	131	3S 1M	3.0%		
O	B	28	1S 2M	10.7%	3.2%	
O	AB	16	0	0.0%		5.76%
O	? (Emergency)	11	0	0.0%		
O	O	248	5S 11M 3Sl	7.7%		
A	A	29	3Sl	10.3%		8.0%
B	B	1	0	0.0%	10.3%	
AB	AB	9	1Sl	11.1%		
		473				

*S, severe.
M, moderate
Sl, slight

Our experience is summarized in Table III.

Reactions were graded as severe, moderate, or mild. Severe (S) indicates a temperature rise of more than 101° and/or a chill. Moderate (M) indicates temperature rise of less than 101° F. Slight indicates very minor and inconsequential symptoms. Hyperpyrexia reactions were most frequent. Two cases of urticaria were recorded. The number of all reactions occurring when type O blood was used to transfuse patients of other types was less than when type specific donors were used. The number of severe reactions in both groups was about equal and approximated 2 per cent although percentages in such a small group are not statistically significant. Only two reactions were potentially serious. Both were stopped after only a few cubic centimeters were given because of dyspnea and anginal pain. Recheck of the donor blood in one case showed that it had been erroneously reported as O whereas it actually was B. The recipient was type A. No cause was found for the second reaction. There were no reactions that persisted more than a few hours.

Summary and Conclusions

Experience with the use of group O blood for all transfusions has proved practical in a 225-bed hospital over an eighteen-month period.

Reactions are no more frequent nor more severe than when type specific blood is used.

Waste is reduced to a minimum.

Bean, William B., Cogswell, Robert, Dexter, Morris, and Embick, James F.: Vascular Changes of the Skin in Pregnancy, Surg., Gynec. & Obst. **88:** 739, 1949.

In an extremely interesting article the authors have analyzed the occurrence of vascular spiders and palmar erythema in 484 white and 759 Negro pregnant women. Vascular spiders were found in 66.6 per cent of the white women and 11.4 per cent of the Negroes. There was a marked increase in the incidence of vascular spiders as pregnancy progressed, a peak being observed just prior to delivery. There was rapid disappearance of these lesions during the postpartum period. The control group of 58 nonpregnant white women showed only a 12 per cent incidence of this phenomenon. The findings in Negro women differed chiefly in the low incidence of these spiders. The occurrence of this lesion was found to be definitely correlated with the amount of skin pigmentation, thus, spiders were more frequent in light blondes than in brunettes.

Palmar erythema was observed in 62.5 per cent of white women and in 35 per cent of Negro women. There was an increase in the incidence of palmar erythema during the progress of pregnancy similar to that seen with the vascular spiders, but not quite so marked. Palmar erythema was almost three times as common as vascular spiders in Negro women, while there was only a slight difference in the incidence of vascular spiders and palmar erythema in white women. The authors felt that the probable cause was the variation in skin pigmentation which was much less deep in the palms than in other areas of skin of Negro women.

LOUIS M. HELLMAN.

A PROPOSED CLASSIFICATION FOR UTERINE AND VAGINAL ANOMALIES

I. W. Monie, M.B., Ch.B. (Glas.), and
L. A. Sigurdson, M.A., M.D. (Man.), Winnipeg, Man.
(From the Department of Anatomy, University of Manitoba)

ALTHOUGH it is virtually impossible to formulate a scheme affording the satisfactory typing of all uterine and vaginal anomalies, a simple international classification, giving clear and concise descriptions, would be of considerable value, especially in the compilation of statistical data.

While many classifications of anomalies of the uterus and vagina are in existence (von Winkel,[1] De Lee and Greenhill,[2] Taylor,[3] Olesker,[4] Way,[5] Jarcho,[6] and others) most of these are unsatisfactory and confusing, being either unnecessarily complex or else oversimplified. Frequently different terms are applied to the same anomaly, the same term is applied to different anomalies, and certain terms are used interchangeably, such as *uterus didelphys* and *uterus duplex, uterus bilocularis* and *uterus septus, uterus arcuatus* and *uterus cordiformis.* Also, the practice, in a few classifications, of compounding Latin, Greek, and sometimes English words to form a descriptive phrase is linguistically undesirable.

Table I. Scheme for Classification of Congenital Anomalies of Uterus and Vagina

Uterus	Corpus (Co)	Nullum	0		
		Simplex	I		
		Duplex	II		
		Arcuatum	Arc		
		Septum	Sep		
		Bicorne	Bi		
		Unicorne	Uni		
	Cervix (Ce)	Nulla	0		
		Simplex	I		
		Duplex	II		
Vagina (V)		Nulla	0		
		Simplex	I	Sagittale	Sag
		Duplex	II	Transversum	Trans
				Coronarium	Cor

Additional Qualifying Terms

Sinistra -trum, (sin): left
Dextra -trum, (dex): right
Immatura -um, (imm): rudimentary
Contracta -um, (contr): narrowed
Imperfecta -um, (imp): incomplete

With the foregoing considerations in mind the authors have devised a simple scheme (Table I) which can be used to classify accurately and concisely a large number of possible anomalies of the uterus and vagina. In classifying a case, the suitable descriptive terms are selected from the list in Table I and are combined with the terms "corpus," "cervix" and "vagina." In this way each case

may be accurately specified, and there is no necessity to fit the anomaly to an unsatisfactory phrase, as may have to be done when using other classifications. To dispense with lengthy phrases, when this is desired, abbreviations for each term are given which may be compounded to construct a descriptive formula. Also included in the table are some additional terms which can be used to enlarge the range of the scheme when necessary, these too having an abbreviated form. For the sake of uniformity Latin has been used throughout.

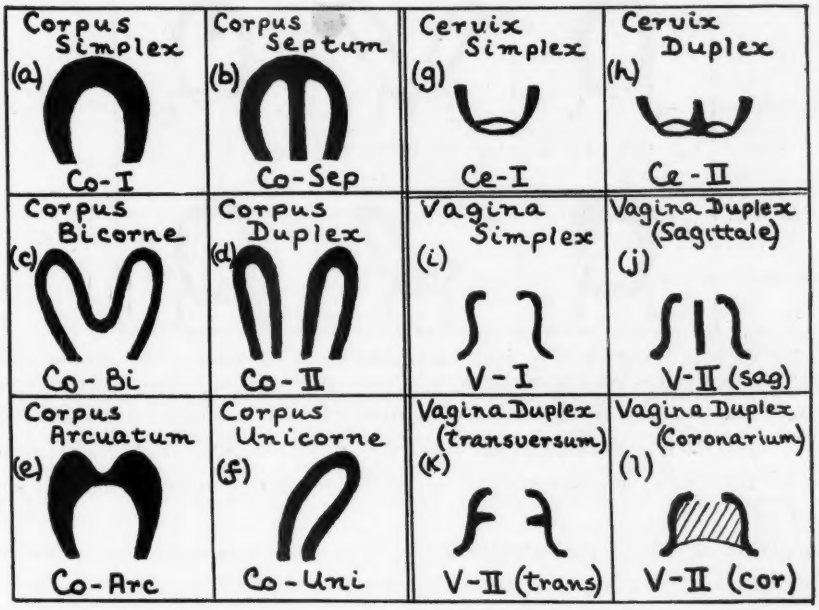

Fig. 1.—Outlines illustrating the principal terms used in Table I.

The definitions of the terms used in Table I are given below. (Note: "Corpus" is a neuter noun; "cervix" and "vagina" are feminine nouns.)

Nulla (-um): the structure is absent, e.g. "corpus nullum," no uterine body.

Simplex: single, as in the normal state (Figs. 1, a, 1, g, and 1, i).

Duplex: double (Figs. 1, d, 1, h, and 1, j). In "corpus duplex" the uterine cavities do not communicate.

Arcuatum: while the fundus of the uterus is notched, the outline of the cavity is normal (Fig. 1, e).

Septum: a septum extends from the fundus of the uterus to the cervix (Fig. 1, b). Where only part of a septum is present the qualifying word "imperfectum" (imp) can be used after septum, replacing the "subseptus" of other writers (Fig. 2, c).

Bicorne: two-horned. The two uterine chambers communicate inferiorly (Fig. 1, c). Where one horn is rudimentary the terms "immaturum" accompanied by "sinistrum" (sin), left, or "dextrum" (dex), right, may be used to qualify "bicorne," thus: Bi (sin. imm.) or Bi (dex. imm.) (Fig. 2, e).

Unicorne: where only one uterus of a "corpus duplex" is present (Fig. 1, f).

While the terms used to qualify "cervix" and "vagina" are self-explanatory, in the case of "vagina duplex" (V.II) it was felt that some indication should be given regarding the position of the vaginal septum which may lie in

the sagittal, transverse, or coronal plane[7] of the vaginal canal. Descriptive adjectives are thus given for these three planes, each being in the neuter case to qualify the understood word "septum" (Fig. 1).

The examples shown in Fig. 2 illustrate the method of using the classification.

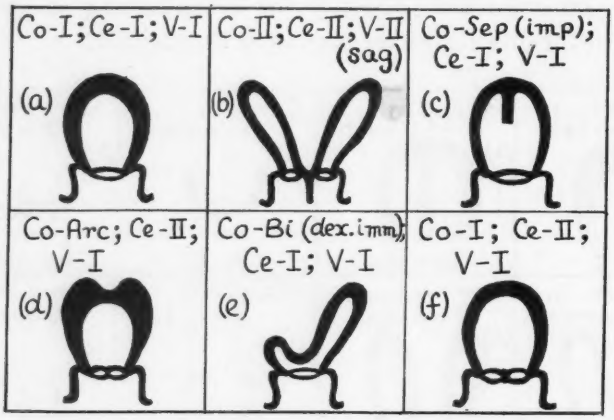

Fig. 2.—Various cases as they would be classified according to the scheme in Table I.
(a) Uterus (corpus simplex et cervix simplex) et vagina simplex.
(b) Uterus (corpus duplex et cervix duplex) et vagina duplex (sagittale).
(c) Uterus (corpus septum imperfectum et cervix simplex) et vagina simplex.
(d) Uterus (corpus arcuatum et cervix duplex) et vagina simplex.
(e) Uterus corpus bicorne (dextrum immaturum) et cervix simplex et vagina simplex.
(f) Uterus (corpus simplex et cervix duplex) et vagina simplex.

Regardless of which classification is being followed, however, details should *always* be given about the uterine body, cervix, and vagina, even where one or two of these structures are normal. Also, it would be of much help if, in every recorded case, a diagram were given depicting the state of the entire uterus and vagina, so that the exact nature of any anomaly would be immediately apparent.

Summary

1. A simple scheme is presented for the purpose of classifying a large number of anomalies of the uterus and vagina.

2. In order to avoid confusion, all available details about the uterine body, cervix, and vagina should always be recorded, even though only one of these structures is abnormal.

We wish to express our thanks to Prof. I. Maclaren Thompson of the Department of Anatomy, University of Manitoba, for helpful advice and criticism.

References

1. von Winkel, F.: quoted by Kermauner in Schwalbe's Die Morphologie der Missbildungen des Menschen und der Tiere, III/2, Kap. 3, S.255, Jena, 1909, G. Fischer.
2. De Lee, J. B., and Greenhill, J. P.: The Principles and Practice of Obstetrics, ed. 9, Philadelphia, 1948, W. B. Saunders Company, p. 471.
3. Taylor, H. C.: Am. J. Obst. & Gynec. **46**: 388, 1943.
4. Olesker, N. H.: Canad. M. A. J. **51**: 51, 1944.
5. Way, S.: J. Obst. & Gynaec. Brit. Emp. **52**: 325, 1945.
6. Jarcho, J.: Am. J. Surg. **71**: 106, 1946.
7. Malkin, S., and Monie, I. W.: In preparation.

A SIGN OF PLACENTAL SEPARATION

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WITH the widespread use of analgesia and anesthesia in obstetrics, the mechanism of labor is changed from the normal to the abnormal in many cases. This is especially true in the third stage.

To counteract this, many obstetricians are using ergonovine intravenously at the time of the birth of the anterior shoulder of the baby. With this innovation, however, the reported incidence of manual removal of the placenta has increased two to four times. The contracting uterus traps the placenta within its cavity.

The purpose of this article is to describe a sign of placental separation that, apparently, has not been emphasized previously and to illustrate how it helps overcome the theoretical rise in the incidence of retained placentas.

One basic point in the physiology of the third stage must be stressed. Separation and expulsion of the placenta are two distinct processes. Separation is not accompanied by any standard well-known sign, while expulsion is characterized by the classical picture described as advancement of the cord, rising of the uterus, bleeding, etc. It is most important to remove the placenta soon after *separation;* otherwise, manual interference becomes increasingly necessary.

A sign of separation that has proved valuable to the author is described.

As soon as the first or second uterine contractions have occurred, the hand is placed on the fundus of the uterus and firm, gentle pressure is exerted in the axis of the pelvic inlet. The other hand is inserted into the vagina. If the placenta is felt with the examining finger in the vagina or in the lower uterine segment, moderate pressure is exerted on the fundus to bring the placenta down to a level where its lower pole can be conveniently grasped by the vaginal hand. By a combination of pressure upward on the fundus and traction from below on the placenta, it is removed. Occasionally one will find that the placenta is still partially adherent, but a short wait for another contraction and then the use of the maneuver described will cause it to be completely separated and delivered easily.

Since 1942, the use of ergonovine at the end of the second stage of labor has been widespread. In the many cases reviewed in the following years, the advantages of the intravenous administration of ergonovine with the birth of the anterior shoulder became apparent. It definitely shortened the placental stage, diminished blood loss, and reduced the incidence of postpartum hemorrhage by at least one-half. The great barrier to its even wider adoption was the increase of incarcerated placentas and the subsequent dangers of sepsis and hemorrhage from this complication.

Fundamentally, if analgesia and general anesthesia are not used, there is no need for ergonovine before the birth of the placenta, and it follows, of course, that there is no need for the sign or the management described herein. Since, however, the great majority of obstetricians use these methods of pain relief, it must then be recognized that an abnormal situation has been produced which requires unorthodox treatment.

Actually, routine vaginal manipulation at the time of placental delivery has not proved dangerous when reasonable care and asepsis were observed. The maneuver described was employed in one thousand cases. The incidence of morbidity was 3.2 per cent uncorrected, which compares most favorably with the general incidence in the four hospitals at which these cases were delivered.

Over 90 per cent of the placentas were delivered within five minutes. In the remaining, longer periods elapsed. In any patient not delivered within twenty minutes, a manual removal of the placenta was performed. The incidence of true manual removal was 2 per cent.

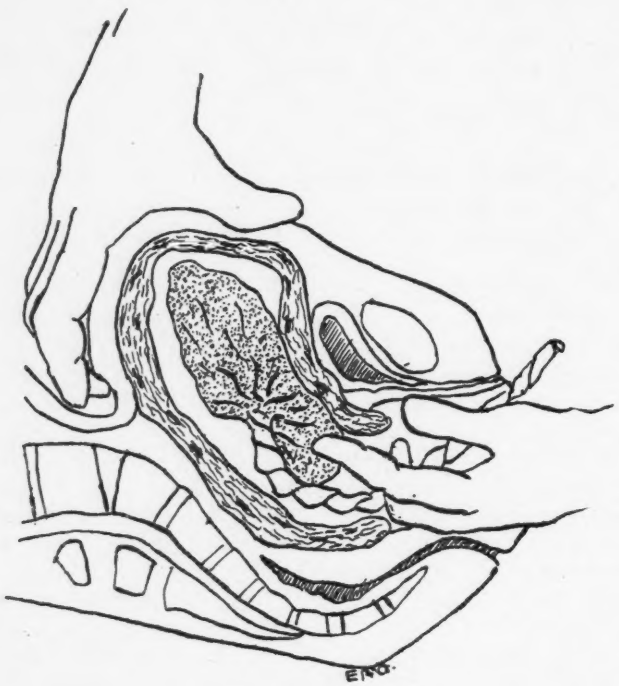

Fig. 1.

The efficacy of this procedure may be judged by the fact that in all these cases, only six cases delivered from below required blood transfusion because of excessive blood loss. In all of these, labor was prolonged, difficult, and terminated operatively. There is no doubt that there was some primary difficulty in the birth mechanism which did not permit the usual, sustained, postpartum uterine contractility. No uterus was packed and no hysterectomies were necessary. There was no maternal mortality.

Finally, the author wishes to emphasize that the sign described is only of particular value if ergonovine is used at the end of the second stage of labor. If the dosage of analgesia and inhalation anesthesia create an abnormal third stage, ergonovine will make the altered physiology approach that seen in natural childbirth. It is under these circumstances that early recognition of separation by the sign described will be of considerable value.

Summary

1. When using ergonovine at the end of the second stage of labor, the mechanism of delivery of the placenta is different. The placenta separates al-

most immediately. It is, therefore, mandatory that it be removed soon after separation, otherwise the incidence of incarceration increases markedly.

2. The classic signs and symptoms of separation of the placenta described in the standard textbooks do not apply when ergonovine is used in the second stage.

3. A simple sign is described which will aid in determining when the placenta is to be delivered. Simple palpation of the placenta within the lower uterine segment when moderate pressure from above is used on the fundus is indicative of placental separation. This is the only reliable sign. Delivery of the placenta by expression or the Brandt maneuver should be carried out forthwith.

References

1. Davis, M. E., and Boynton, M. W.: Am. J. Obst. & Gynec. **43**: 775, 1942.
2. Adair, F. L.: Maternal Care, 1937, U. of Chicago Press, p. 64.
3. O'Conner, C. T.: Am. J. Obst. & Gynec. **48**: 603, 1944.
4. Diddle, A. W.: Am. J. Obst. & Gynec. **43**: 450, 1942.
5. Roberts, P. A.: Am. J. Obst. & Gynec. **43**: 849, 1942.
6. Dieckmann, W. J. et al.: Am. J. Obst. & Gynec. **54**: 415, Sept., 1947.

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Tyler, Edward T.: Use and Misuse of Endocrine Therapy in Sterility, J. A. M. A. **139**: 560, 1949.

The author found that endocrine causes contribute only 20 to 25 per cent of involuntary sterility. Probably one of the most frequently treated functional disorders in infertility is failure of ovulation. Endocrine therapy of anovulation has not been too successful. Preparations containing large amounts of follicle-stimulating hormone are most valuable. The use of preparations containing pregnant mare's serum has been disappointing to the author. A hypoplastic uterus is frequently a feature in a generalized state of hypogonadism. Development of the hypoplastic uterus can be induced by estrogenic therapy and the dosage should be heavy. Poor corpus-luteum function may be another factor.

The treatment of habitual abortions with endocrines has also been disappointing, indicating a lack of knowledge of the etiology of this condition.

From the scientific point of view, thyroid should be given only in cases of hypothyroidism which is based on the basal metabolism rate, blood cholesterol, and blood iodine. There is a definite question as to the value of its routine usage.

In the male the two major conditions in which hormones may be involved are (1) impotence, and (2) defective spermatogenesis. In impotence testosterone propionate may be of some value. Neurogenic and psychogenic factors may be of some importance. Hormonal stimulation of sperm production is not encouraging. In cases where the sperm count is fairly normal but motility is impaired, small doses of testosterone may be of some benefit. Thyroid should be used in cases of hypothyroidism. William Berman.

Department of Book Reviews

EDITED BY PHILIP F. WILLIAMS, M.D., PHILADELPHIA, PA.

Review of New Books

This **Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix**[1] in its fifth volume presents a statement of the results obtained in 1941 and previous years which were collated in 1948. This report is the first since 1941, and includes statements from twenty-four radiotherapeutic centers in eight different countries, including five from the United States. It is apparent that future reports will be extended to include the analysis of matter relating to corpus uteri and vagina, as well as results obtained by combined surgical and radiotherapeutic treatments of the cervix. Only those series of cases in which all clinical diagnoses have been microscopically confirmed, can, as a rule, be accepted.

A working classification of cancer cases in which different portions of the uterus are involved singly or in multiple is given as well as a suggestion for classification for cancer of the vagina. The statements from the various radiotherapeutic centers form the bulk of the text. Radiotherapeutic treatment of cancer of the cervix of the entire group showed a five-year cure rate of 37.8 per cent. In Stage I the rate was 62.5 per cent, and the cure rate dropped to 9.1 per cent in the Stage IV group.

This annual report and the atlas illustrating the division of cancer of the uterine cervix should be of interest and value to all clinics treating cervix cancer with radium. An adherence to the rules and regulations regarding the classification should soon present uniform and comparable statistics from even small clinics to determine the treatment necessary to produce a more favorable cure rate. PHILIP F. WILLIAMS.

This book by Dr. Tauber is devoted to the problems of the **Gynecologic Diagnosis.**[2] He offers the text to focus attention on the subject, feeling that in many of the large textbooks, the discussion of diagnosis is often buried under a mass of miscellaneous information.

The first part of the book is concerned with methods and technique. A detailed and well-illustrated method of physical examination of abdominal and pelvic organs is presented. Tauber stresses the importance of rectal examination in gynecologic examination. The text is direct and concise on the usefulness of routine, special, and postoperative laboratory tests for diagnostic purposes. Diagnostic surgical procedures consider the frequently used minor operations, biopsy of the cervix to roentgenographic study of the urinary tract.

One hundred seventy pages of the text are devoted to a discussion of the diagnostic problems in five groups of classes. First group points to a characteristic history, the second group necessitates, in addition, an adequate and expert physical examination. The third group has cases with uncharacterized histories but with characteristic signs. The fourth group illustrates the need for special laboratory work in addition to history, physical and laboratory findings, while the final group illustrates such extreme difficulties that the diagnosis must be regarded as only putative and made final only by exploratory operation or surgical pathology report.

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[1]**Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix.** Fifth volume, statements of results obtained in 1941 and previous years. Sponsored by The British Empire Cancer Campaign, London, The Donner Foundation, Philadelphia, the Cancerforeningen, Stockholm, The World Health Organization. Editorial Committee: Dr. J. Heyman (Editor), Stockholm, Dr. M. Donaldson, London, and Dr. L. S. Scheffey, Philadelphia.

Kungl, Boktryckeriet. Stockholm, 1949, P. A. Norstedt & Soner.

[2]**Gynecologic Diagnosis.** By Robert Tauber, M.D., F.A.C.S., F.L.C.S., Associate in Gynecology and Obstetrics, the Graduate School of Medicine, University of Pennsylvania, Diplomate, American Board of Obstetrics and Gynecology. 264 pages with 80 illustrations. New York, 1949, Thomas Nelson & Sons.

The book closes with a very practical discussion of how to prevent errors in gynecological diagnosis. The book may be commended for use of students and residents, as well as for those who may be preparing for a demonstration of their ability of pelvic diagnosis before certifying boards. PHILIP F. WILLIAMS.

In the second edition of **Essentials of Gynecology**[3] the authors have revised the discussion of the technique and nursing procedures in gynecology, in line with the changes made during the past eight years in the operating rooms of Johns Hopkins Hospital. They have also incorporated in the text reference to significant advances in gynecology. A new chapter on radiation therapy in gynecology by Dr. Bernard Brack has been added.

The first nine chapters on Anatomy, Physiology, and Disease, form a concise but clear discussion of the basic subject matter. Four chapters are devoted to gynecological surgery and should give the student nurse an excellent idea of what goes on in the operating room and recovery period and her relation to the surgeon and the patient. These chapters thoroughly describe the technique of the Hopkins Clinic and the pre- and postoperative handling of the patient.

The chapter on radiation therapy should give the nurse sufficient information of the use of radium and of her duties in the care of a radium patient during the treatment. This well-written manual should be helpful to nurses interested in gynecologic nursing.

PHILIP F. WILLIAMS.

Dr. Hamblen has written this book, **Facts About the Change of Life,**[4] with the feeling that education of the patient in physiology, hygiene, and in medical problems is a fundamental part of a patient-physician relationship. The book is simply and directly written, and discusses for the laity the anatomy and physiology of a woman's pelvic organs, and the associated glands of internal secretion. The text discusses for the patient the changes which occur to bring about the cessation of pelvic functions, and informs her physician how he may enlighten the patient as to the underlying causes of jittery nerves and mental quirks. The author discusses for the lay person the anatomic sequelae of sexual involution and gives a common-sense discussion of malignancy. He feels that estrogen treatment of the menopause should be very limited in its duration, that the psychology of estrogen injections is bad, that only a minority of women undergoing the menopause require such treatments. He states that estrogen properly used is a boon, but improperly given may prove a curse. This book may be recommended unhesitatingly to the woman approaching or undergoing her change of life. PHILIP F. WILLIAMS.

Dr. I. Harvey Flack has written an interesting and thoroughly documented story of **Lawson Tait,**[5] a stormy petrel in British surgery. The book is an expansion of the Thomas Vicary lecture of the Royal College of Surgeons for 1947. Dr. Flack has extensively searched the records for previous unpublished items regarding Tait, as well as studied previous biographical sketches of this remarkable figure. Discussing Vicary's definition of a surgeon, he writes that Tait would have scored on three of Vicary's four requisites, in that he was learned, expert, and ingenious, but that he was not invariably well mannered.

The story carries through Tait's early days as a student and assistant, with side lights on the men with whom he was associated, particularly in regard to the legend that he was an illegitimate son of Sir James Y. Simpson. From the beginning of his special practice in Birmingham, he was in immediate conflict with his confreres, showing them a remarkable want of respect for age and authority. Flack discusses Tait's early operative techniques, his substitution of the ligature for the extraperitoneal clamp in ovariotomy, his

[3]**Essentials of Gynecology.** By Leo Brady, M.D., F.A.C.S., Assistant Professor of Gynecology, Johns Hopkins University, and Ethna Louise Kurtz, R.N., Formerly, Head Nurse, Brady Urological Institute, Johns Hopkins Hospital, and Eileen McLaughlin, B.S., R.N., Instructor and Supervisor, Gynecological Nursing, Johns Hopkins Hospital. Second Edition, 248 pages with 55 illustrations, New York, 1949, The Macmillan Company.

[4]**Facts About the Change of Life.** By E. C. Hamblen, M.D., F.A.C.S., Professor of Endocrinology and Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine. 86 pages with 6 illustrations. Springfield, Ill., 1949, Charles C Thomas.

[5]**Lawson Tait, 1845-1899.** By I. Harvey Flack, M.D. 139 pages, illustrated. London, 1949, William Heinemann, Ltd.

pioneer work on the gall bladder, and what is probably his best-known surgical advance, the prompt removal of ruptured tubal pregnancy. As his case lists increased, he became a constant reporter of his work and at every opportunity attacked vigorously all who differed with him.

It is interesting that Tait was opposed to the use of animals in research surgery. His famous quarrel with his old friend, Sir Spencer Wells, is discussed, as well as his attitude toward the discoveries of Lord Lister and Pasteur. His acme and his death are well portrayed. Dr. Flack has given us a fine picture of this brilliant surgeon and fine writer—a domineering and pugnacious personality in the development of gynecology in England.

PHILIP F. WILLIAMS.

In the first chapter of this book, **Ectopic Pregnancy,**[6] Masani observes that perhaps the most fascinating condition in gynecology is that of extrauterine pregnancy. In his history of the lesion, first noted by Albucassis in the middle of the eleventh century, he covers the evolution of extrauterine pregnancy throughout the years to our present concept of etiology, diagnosis, and treatment. In a masterly description, he brings out the succeeding discoveries of the various types of extrauterine pregnancy and the advances in our knowledge of the condition.

He offers a classification of predisposing factors and supports claims for them in his excellent description of pathology of various types of extrauterine pregnancy. There is an excellent section on differential diagnosis. Some truly unusual instances of ectopic nidation are referred to in this chapter. He recounts the pioneer surgical treatment of lesion, the choice of anesthetic, and stresses the subject of blood transfusion. He feels that surgical advances, prompt operation, and the availability of prompt and sufficient transfusions should still further reduce the declining mortality rate. He states that at least one-third of the women who have had extrauterine pregnancy will conceive and a large proportion of them should have normal pregnancies and deliveries.

The book closes with a series of case histories of atypical sites of nidation. The American literature has been most extensively quoted. Presumably, the author feels that competent operators do not need illustrations of operative technique. He has described only in general terms the surgical steps necessary for the various types of extrauterine pregnancy which may be encountered.

PHILIP F. WILLIAMS.

Dr. Titus has rearranged the subject matter and added new sections on pregnancy, antepartum care, analgesia and anesthesia in the second edition of his **Atlas of Obstetric Technic.**[7] There is new matter in the sections on pelvimetry and on forceps delivery. The legends of a great many of the illustrations have been modernized.

The book profusely portrays the subject of operative obstetrics and the detailed steps in procedures are much more numerous than in the usual text. The book makes an exceptionally vivid way of presenting to the student or practitioner what actually happens in a particular operative delivery.

Very properly, there have been added illustrations of the treatment of sterility which is regarded as an obstetric problem, as well as the treatment of minor postpartum complications, the techniques of sterilization, and treatment of suppurative mastitis, while the popular methods of analgesia and anesthesia are illustrated and briefly discussed. One feels, however, that cyclopropane mentioned as conventional for late first stage and second stage and delivery by inhalation brings the patient repeatedly within range of explosibility.

This atlas should be in continued favor because of the excellent pictorial presentation of what one may have to do in a complicated obstetrical case. It seems appropriate that credit for the fine illustrations, by E. M. Shakleford, should be mentioned in the review.

PHILIP F. WILLIAMS.

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[6]**Ectopic Pregnancy.** By K. M. Masani, M.D. (Lond.), F.R.C.S. (Eng.), Honorary Lecturer in Gynaecology and Obstetrics, Seth Gorhandas Sunderdas Medical College, Bombay. 161 pages. Bombay, 1949, The Popular Book Depot.

[7]**Atlas of Obstetric Technic.** By Paul Titus, M.D., Obstetrician-Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh. Second Edition. 194 pages with 203 illustrations. St. Louis, 1949, The C. V. Mosby Company.

Dobbie's **Obstetrics and Gynecology**[8] is a book packed with excellent advice to the general practitioner for whom it was written.

The larger part of the manual, 222 pages on obstetrics, omits anatomy and physiology and goes at once into the complications of pregnancy. The discussions are clear and succinct. Cesarean section is advised as a routine in diabetes. Under toxemias, the author makes the statement that the high-protein diet treatment of toxemia has been abandoned. She advocates conservative treatment of pregnancy with severe heart disease as it has a lower mortality than section, which, however, she prefers in all pregnant cardiac patients if any obstetric complication arises. Discussing home obstetrics, she expresses the feeling that the frequent mediocrity of obstetrics in general practice is due to the attempts to do what in any case is better done in a department equipped for the purpose. There is fully detailed and illustrated instruction for both normal deliveries and emergency abnormal situations in the home. The difficulties of labor are treated in much the same manner as in this country. The author is repetitious in her warnings against the injudicious use of chloroform.

In the section dealing with gynecology, the author wisely omits anatomy and pathology and denotes considerable space to symptoms, examination, diagnosis, and medical treatment, and stresses the need for speculum examination in all cases, and biopsy in bleeding cases. Where no cause for infertility is detected, thyroid is the favorite therapy. Displacements, benign tumors, infections, and other conditions are discussed as to diagnosis and the indications for operation.

In the section on radiotherapy in gynecology, there is an ample discussion of cancer, as well as the use of radiotherapy in nonmalignant conditions. There are timely chapters in each of the main sections on how to tell the patient the information she should have on diagnosis or suggested therapy.

This clear and concise exposition of the principles of the two topics, with a frequent personal tone, and often a didactic manner, should help many a family physician to improve his knowledge and methods.

PHILIP F. WILLIAMS.

The small accomplishment in recent years in the reduction of infant mortality in the first few days of life and the fact that the majority of neonatal deaths are attributable to the premature births, makes welcome this new edition of Hess and Lundeen, **The Premature Infant, Medical and Nursing Care.**[9] Eight years have elapsed since the first edition was published, during which time many advances have taken place in the care and treatment of prematurely born infants.

The authors discuss the minimum requirements for premature infant stations, in comparison to nurseries for full-term infants. In this chapter they state the principles of nursing technique and the qualifications and need for continued nursing personnel. Various types of incubators are described, illustrated, and evaluated. The premature infant station (Michael Reese Hospital) is described in detail. A new section has been listed by the authors on the common breaks in technique which may occur in premature care routine.

There is a chapter on the transportation of the premature child from homes or the hospital to such stations and a very complete outline of domiciliary care is given. In the follow-up care of premature infants at the Michael Reese Hospital, such infants have a separate clinic entirely apart from the sick or well baby clinic. Stress is laid on the use of breast milk nutrition. There are chapters on artificial feeding and feeding techniques and the need and dosage of vitamin supplements.

There is a liberal discussion of the therapeutic measures, transfusion, oxygen, gavage, and other methods used to promote continuance of life, as well as an excellent discussion of the medical therapeutic agents, particularly the antibiotics. In the latter section, the

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[8]**Obstetrics and Gynaecology, A Synoptic Guide to Treatment.** By Beatrice M. Willmott Dobbie, M.A., M.B., F.R.C.S., D.M.R.E., Honorary Surgeon, Birmingham and Midland Hospital for Women, Honorary Surgeon, Birmingham Maternity Hospital. 348 pages with 22 illustrations, New York, London, 1949, Paul B. Hoeber, Inc.

[9]**The Premature Infant, Medical and Nursing Care.** By Julius H. Hess, M.D., Professor Emeritus, Department of Pediatrics, University of Illinois College of Medicine; Senior Attending Pediatrician, Michael Reese Hospital, and Consulting Pediatrician, Cook County Hospital, and Evelyn C. Lundeen, R.N., Supervisor, Premature Infant Station, Sarah Morris Hospital Station of Michael Reese Hospital Chicago. 359 pages, 101 illustrations. Second edition, Philadelphia, 1949, J. B. Lippincott Company.

toxic manifestations of such agents are clearly described. Among the diseases of the special organs and the systems, there is much new matter on erythroblastosis fetalis, anemia, and infections. The authors have devoted considerable material to the subject of syphilis in maternity.

Their observations in their follow-up clinic work have led to an excellent consideration of the later physical and mental development of premature infants. They outline the orientation and instruction of nursing personnel for premature stations, small hospital services, or public health personnel.

At the present time they note that not only is there increasing federal interest in this problem but that many cities and twenty-eight of forty-eight states have more or less complete plans in operation for improving the case of premature infants. They discuss these plans and compare them, particularly with regard to minimum facilities in institutions for providing transportation, breast milk nutrition, and trained personnel.

The revision of the book and the many additions should insure the position of this book as an outstanding text and guide in the many-sided problem of the premature infant.

PHILIP F. WILLIAMS.

In **Having Your Baby,**[10] Dr. Biskind has offered a small book to inform women as to prenatal care, and to alleviate anxiety during pregnancy. The subject matter of prenatal hygiene, the discussion of labor and delivery and postpartum care carry a woman from the time of conception until she begins her annual pelvic examinations in a logical sequence. Each section has a series of numbered simple factual statements or instructions. The reviewer does not recall any question ever asked by a maternity patient which is not answered in this book; and answered in such a succinctly scientific and definite form that a reading of the book by a pregnant woman should shorten office consultations. It is one of the best of many excellent manuals of this character which the obstetricians of this country have prepared for use of patients. It is highly recommended.

PHILIP F. WILLIAMS.

Dr. Baruch has presented in **New Ways in Discipline, You and Your Child Today**[11] her interpretation of modern pediatric psychology and psychiatry to parents, teachers, and physicians.

From infancy to adolescence, the various problems of the child are enumerated and discussed. According to Dr. Baruch, children are not so frequently bad as badly hurt. And, again what we call adolescent disobedience is often nothing more than a child's normal growth toward independence. She stresses the use of those activities which have psychological value in connection with discipline.

The influence of radio rackets, movie murders, and killer cartoons on behavior leads to situations in which she urges changing the emotions and activities into more normal outlets. The relationship of parent training ond school guidance and the part a family physician may play are discussed.

Such a book as this with its suggestion of adaptation of modern methods of psychology to the problems of childhood should be widely read by both parents and teachers.

PHILIP F. WILLIAMS.

The second edition of **Geriatric Medicine, The Care of the Aging and the Aged**[12] by a list of outstanding contributors has been revised and rewritten. The present trend in population age groups has increased in importance and degree our attitude toward problems of changing physiology and of disease in the upper decades of life.

The text is divided into a general consideration of aging and senescence followed by a more detailed discussion of metabolic diseases, and the normal senile and the patho-

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[10]**Having Your Baby.** By Leonard H. Biskind, M.D., Acting Director, Department of Obstetrics and Gynecology, Mount Sinai Hospital, Cleveland, Ohio. 91 pages. Portland, Oregon, 1949, Western Journal of Surgery Publishing Co.

[11]**New Ways in Discipline.** By Dorothy Walter Baruch. 268 pages, illustrated. New York, 1949, Whittlesey House, McGraw-Hill Book Company, Inc.

[12]**Geriatric Medicine, The Care of the Aging and the Aged.** Edited by Edward J. Stieglity, M.S., M.D., F.A.C. P., Attending Internist, Suburban Hospital, Bethesda, Maryland, (Chairman Staff, 1945-47); Doctors Hospital, Wash., D. C. 773 pages with 180 figures. Second edition, Philadelphia, 1949, W. B. Saunders Company.

logical lesions of the aged according to the various systems. To the readers of this JOURNAL, particular interest should be in the chapters on dysfunction of the endocrine glands by N. S. Davis, III, and on geriatric gynecology by E. C. Hamblen. In the latter is a particularly fine discussion of the menopause, and its handling.

The editor states in the preface that geriatric medicine should not be regarded as a specialty, but rather an application of understanding of the changes which come with senescence to all the facets of medical practice, not to add years to life but life to years. The volume should be of value, in many senses of the word, to all physicians.

PHILIP F. WILLIAMS.

The psychosomatic concept in medicine has been widely accepted in the six years since the first edition of this book, **Psychosomatic Medicine,**[13] appeared. Medical experience in the military services has probably done much to stimulate interest in the subject. There has been a general rearrangement in the first part, while the second part of the book applies this new principle to special problems. To the obstetrician or gynecologist in his daily contact with worried and anxious women, the book offers considerable discussion and suggestions for help in the problems which constantly confront him from a woman in her first pregnancy to her postmenopausal neuroses. Much material of value is found in the early chapters on psychotherapy in the newly married woman or in the menopause, marital adjustment, and physiology of pregnancy. The psychological background of sexual functions is well discussed in Chapter 17. A reading of this matter should certainly assist physicians in the handling of marital maladjustments. A study of such appropriate points of the book should promote a more favorable understanding in a patient-physician relationship, and effective treatment in those cases where emotional factors add to the burden of physical disease in women.

PHILIP F. WILLIAMS.

Physiology in Diseases of the Heart and Lungs[14] by Altschule is the most recent of a series of monographs on medicine from Harvard University. The text has been developed from lectures delivered to both undergraduate students and postgraduates who desired a review and reorientation of this basic science as they engaged in the problems of clinical medicine.

The author has reviewed and analyzed many physiologic studies on the heart and lungs with reference to various lesions of the systems, the mechanism by which symptoms and objective findings are produced, and the manner in which effective therapy may be secured. To each section a bibliography has been appended. Such a review of the data on physiological bases of the diseases of these two systems should be of interest to those practicing clinicians who have continued an interest in the underlying mechanisms of disease.

PHILIP F. WILLIAMS.

The material incorporated in this book, **Parathyroid Glands and Metabolic Bone Disease,**[15] represents a partial summary of the studies on calcium metabolism carried out in the Metabolic Ward of the Massachusetts General Hospital over a period of twenty-four years. These studies may be regarded as reflecting the advances in our knowledge of calcium metabolism over that period, and they reflect the personal opinions of the authors as to their present significance.

The first four chapters discuss the normal and pathologic physiology of the parathyroid glands and their clinical variations, hyper- and hypoparathyroidism, as well as

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[13] **Psychosomatic Medicine, The Clinical Application of Psychopathology to General Medical Problem.** By Edward Weiss, M.D., Professor of Clinical Medicine, and O. Spurgeon English, M.D., Professor of Psychiatry, Temple University Medical School. Second edition. 755 pages. Philadelphia, 1949, W. B. Saunders Company.

[14] **Physiology in Diseases of the Heart and Lungs.** By M. D. Altschule, M.D., Assistant Professor of Medicine, Harvard Medical School; Visiting Physician and Research Associate, Beth Israel Hospital; Director of Internal Medicine and of Research in Clinical Physiology, McLean Hospital. 354 pages. Cambridge, Mass., 1949, Harvard University Press.

[15] **The Parathyroid Glands and Metabolic Bone Disease, Selected Studies.** By Fuller Albright, A.B., M.D., Associate Professor of Medicine, Harvard Medical School, Boston, Mass.; Physician, Massachusetts General Hospital, Boston, Mass., and Edward C. Reifenstein, Jr., A.B., M.D., F.A.C.P., Consultant-in-charge, Department of Clinical Investigation, Sloan-Kettering Institute of Cancer Research, Memorial Hospital Cancer Center. New York. 332 pages with 157 illustrations and figures. Baltimore, 1948, The Williams and Wilkins Company.

the relation of vitamin D to the metabolism of calcium. In the following chapters metabolic bone disease is discussed generally, with the specific problems of osteoporosis, osteomalacosis, osteitis fibrosa, and Paget's disease thoroughly analyzed.

Pregnancy is one of the four well-recognized conditions in which hyperplasia of the parathyroid glands is encountered. This condition according to the authors has a tendency to a low serum calcium value and it seems not improbable to them that the normal stimulus to parathyroid hormone production is a serum calcium value below normal. Twice as many cases of clinical hyperparathyroidism occur in women as in men.

Postmenopausal osteoporosis is regarded as extremely common. In their study of this lesion regarding the therapeutic use of estrogens, it was considered that the two forms used (Estradiol benzoate and diethylstilbestrol) decreased the calcium and phosphorus excretion, both fecal and urinary. The two agents were equally effective. Their dosage schedule is given. Androgens likewise decreased the Ca and P excretion. Progesterone had no effect whether given alone or in combination with estrogen. The effect of a combined therapy with estrogen and androgen on calcium was greater than either alone. The authors further discuss certain therapeutic aspects concerning postmenopausal osteoporosis, as well as ovarian agenesis and other forms of congenital hypoestrinism.

The volume may be regarded as reflecting the present status of study of the parathyroid glands and calcium metabolism.

PHILIP F. WILLIAMS.

In this comprehensive book, **Medicine Throughout Antiquity,**[16] Dr. Gordon reviews an age of medicine not usually dwelt upon in medical histories. In a scholarly but not pedantic manner, he presents evidence of the earliest traces of medicine found in archeological ruins and in such discoveries as the recently unearthed cave pictures in France, and systematically carries his subject through the Assyro-Babylonian and Egyptian legends and earliest mention of medical thought.

In this section of prehistoric and protohistoric medicine he recounts the development of healing of many of the eastern civilizations, Persian, Indian, Chinese and Amerind. A section on the Hebrew medicine is complete with quotations from and references to both the Old and New Testaments, including the first recorded instance each of birth control and of infertility. The second section of his book deals with the rather better recognized Greco-Roman period with its various schools of philosophy and practice. The Romans and Greeks, it is noted, had both socialized medicine and hospitals.

This book should have a wide appeal, not only to those who are historically minded in medicine, but equally to those who are interested in human cultural history.

PHILIP F. WILLIAMS.

This is the first volume of three which are to constitute the **Atlas of Mahfouz's Obstetric and Gynaecological Museum.**[17] It is, I believe, the first presentation of its kind in any literature embodying such a wealth of pathological, gynecological, and obstetrical material removed surgically and at autopsy. The subject matter is divided into twenty-three chapters dealing with special phases of obstetrical and gynecological pathology. It includes a description of the specimens which have been magnificently reproduced, 219 in full-color plates and 217 in black and white. The author has taken the pains of detailing salient medical and surgical data which help to give the "advanced student ambitious to specialize in gynecology and obstetrics" a clear picture not only of the pathological entities but also of their clinical implications. Out of the wealth of his clinical and surgical experience in the two specialties, Mahfouz has drawn principles and explanations not commonly met in the ordinary textbooks. His tracing of the historical development of present-day concepts of diseases illustrated by his specimens is not the least valuable feature of this monumental work.

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[16]**Medicine Throughout Antiquity.** By Benjamin Lee Gordon, M.D., Member American Association of the History of Medicine and American Academy of Ophthalmology and Otolaryngology. 793 pages with 157 illustrations. Philadelphia, 1949, F. A. Davis Company.

[17]**Atlas of Mahfouz's Obstetrical and Gynaecological Museum.** By Naguib Pacha Mahfouz, M.CH., F.R.C.O.G. (Hon.), F.R.C.P. (London), F.R.C.S. Eng. (Hon.). Volume I. Altrincham, England, 1949. John Sherratt and Son.

The twenty-three chapters constituting this book deal for the most part with anatomical structures and pathological conditions including malformations of the female genital organs, prolapse of the pelvic organs, menstruation and functional disturbance, the pituitary gland during pregnancy, disorders of pregnancy, accidents of labor and diseases of the puerperium, benign and malignant tumors of the uterus, ovarian tumors, fetal malformations of obstetrical importance, and antenatal and intranatal causes of fetal death.

Professor Mahfouz has made a unique and invaluable contribution to gynecology and obstetrics. Not only advanced students but specialists of extensive experience will want to add this volume to their medical libraries. Although the views expressed may differ from the reader's experience here and there, the author's rich experience and judgment are so abundantly manifest throughout the volume as to more than make up for minor disappointments or deficiencies. The perusal of the book leaves one with the anticipated pleasure of looking forward to the appearance of the next two volumes. I. C. RUBIN.

This textbook of gynecology by Albert Netter[18] is one unit of the medical-surgical collection annually revised and published by the Flammarion Press of which Professor Pasteur Vallery Redot is the director general. It is in loose-leaf form which permits of insertion of leaves of text to be added annually reflecting the results of latest research in the field. It is evidently intended for the practitioner and student and for the busy specialist who wishes to scan any particular chapter or pathologic entity that may interest him. The context in general satisfies these desiderata. The subject matter is clearly and systematically presented. There is much sound judgment in debatable subjects, the viewpoint and objective being focused on useful clinical practice. The field of gynecology is covered quite comprehensively although briefly in some chapters. Inasmuch as the volume is intended for the practice of office gynecology, operative technique is not described except here and there and sketchily. However, operative indications and contraindications and types of surgical procedures are discussed and their value compared with medical and physiotherapeutic treatments.

There are a number of omissions which American and English gynecologists will not fail to note, as for example the Manchester or Fothergill operation for prolapse of the uterus, mention of radiopaque solutions for hysterography, the renewed radical treatment of cancer of the cervix, the Papanicolaou smear, the newest antibiotics such as aureomycin and dihydrostreptomycin. The present reviewer could take issue with the author's treatment of kymographic uterotubal insufflation and his conclusions regarding this and hysterosalpingography. One could find fault with the provincial restriction of authors although it is easy to understand national preferences.

Especially useful and valuable are the chapters on functional genital troubles and the description of ovarian tumors. Considering the relative limitations of the scope of the book, these subjects have been accorded textual treatment worthy of more exhaustive treatises.

As the author states in the preface, it is intended to add subject matter each year which has been culled shortly after the book's publication. It is suggested that the term *bibliography* be changed to *references*, as in many chapters enumeration of three or several more cannot be said to constitute the bibliography. I. C. RUBIN.

Blakiston's New Gould Medical Dictionary[19] is based upon the widely known work of the nestor of dictionary makers, Dr. Gould, whose original dictionary has gone through many editions since its first publication in 1890. However, the progress of medicine in these recent decades has demanded a new survey, and a critical examination of world literature for the many new terms and procedures which have been developed during the period. The

[18] **Gynecologie.** By Albert Netter. Paris, 1949, Editions medicales Flammarion.

[19] **Blakiston's New Gould Medical Dictionary,** Edited by Harry Wellington Jones, M.D., Colonel, U. S. Army, retired, Contributing Editor, **Encyclopedia Americana,** Former Director, Army Medical Library, Washington, D.C.; Normand L. Hoerr, M.D., Ph.D., Professor of Anatomy, School of Medicine, Western Reserve University; Arthur Osol, Ph.D., Professor of Chemistry, Director of Chemistry Department, Philadelphia College of Pharmacy and Science, Editor-in-Chief, **United States Dispensatory.** With the assistance of an editorial board and over 100 contributors. First Edition. 252 illustrations. 129 in color. 1294 pages. Philadelphia, 1949, The Blakiston Company. Textbook edition $8.50. Thin paper edition $10.75. DeLuxe edition $13.50.

services of a large staff have been called upon to encompass all of this varied material and the task has been accomplished most satisfactorily in this valuable addition to the American medical literature. The book is well printed, beautifully illustrated by a series of colored plates, and in its 1204 pages constitutes an exhaustive presentation covering all branches of medicine and the allied sciences. It should be in the library of every physician.

GEORGE W. KOSMAK.

The second edition of the valuable **Atlas of Surgical Operations**[20] by Cutler and Zollinger appears after an interval of ten years during which many significant advances have been made in this field of medical practice. New and better methods of anesthesia have been developed, as well as of pre- and postoperative care, the treatment of shock, and the control of sepsis. But all of these do not constitute a substitute for meticulous surgical technique, to the attainment of which this manual is largely directed. The revised edition includes an additional thirty new procedures and almost half the illustrations have been revised and redrawn.

Although directed to interns and residents in hospitals, the masterly presentation of the subject matter should constitute a valuable reference manual for all general surgeons as well as gynecologists, for the closing chapter is devoted to pelvic surgery.

The book should have a wide reception and constitutes a classic contribution to American medical literature.

The work also constitutes a memorial to the senior author who died unfortunately before its completion and had always maintained an active interest in the development of the young surgeon.

GEORGE W. KOSMAK.

[20]**Atlas of Surgical Operations.** By Elliot C. Cutler, M.D., and Robert M. Zollinger, M.D. Illustrated by Mildred B. Codding, A.B., M.A. Second Edition. New York, 1949, The Macmillan Company. Price $9.00.

Di Cio, Alfredo V., and Schteingart, Mario: Serum Gonadotropin in the Treatment of Intermittent Claudication, Prensa méd. argent. 33: 2099, 1946.

The authors, of the National Academy of Medicine of Argentina, selected 19 cases of intermittent claudication and treated them only with a series of 18 to 20 injections of serum gonadotropin (for a total of 9,000 to 10,000 I. U.) each over a period of three weeks, i.e., 500 I. U. per day.

Among the 19 cases, 6 very favorable results were obtained, 11 patients experienced favorable relief of variable lengths of time and in 2 cases little benefit was seen. In the favorably responding cases it was observed that the patients also noted a general improvement of their sexual potency and their general well-being and there were increases, in some, of excretory andogens.

C. E. FOLSOME.

Correspondence

Evaluation of Radiotherapy

To the Editor:

As a radiologist, I am in the habit of reading many journals in allied fields, a practice in which I sometimes find myself woefully in arrears. It is thus that I have but recently read the article by Speert and Peightal entitled, "An Evaluation of Adjunctive Radiotherapy in the Surgical Treatment of Endometrial Carcinoma," which appeared in the September, 1948, issue of the JOURNAL. The conclusion drawn in this article serves only further to becloud the issue of the procedure of choice in the treatment of corpus carcinoma. I therefore feel constrained to write this letter in an effort to clear the field.

In this article, the authors divide corpus carcinoma into three stages on a *histologic* basis: early, where the carcinoma is limited to the endometrium or where invasion of the myometrium is minimal; intermediate, where not more than half the thickness of the uterine wall is invaded; advanced, where more than half the thickness of the myometrium is involved. The five-year determinate (i.e., based on the traced cases) survival rate on the basis of these stages is then given in their Table VI as follows:

	EARLY		INTERMEDIATE		ADVANCED	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Hysterectomy	33	85	25	52	14	29
Hysterectomy plus x-ray, (with or without radium)	7	71	7	57	14	57
Hysterectomy plus radium (with or without x-ray)	24	79	3	67	2	0

Since, as seen from this table, there is no apparent benefit from either preoperative radium or postoperative x-ray in the early stage, the authors conclude that hysterectomy alone is the procedure of choice in corpus carcinoma, except that in the advanced stage an advantage seems to result from postoperative x-ray.

It is to this error in conclusion that I wish to draw attention. Since the division into stages is on a histologic basis, hysterectomy alone as the procedure of choice can be advocated only if one can determine the degree of invasion of the myometrium at the time the patient is examined and a curettage is done. It is at this time that an opinion must be given as to the procedure of choice—and not later, after removal of the uterus and its histologic examination. There is no means of determining the extent of involvement of the uterine wall by a corpus carcinoma from the tissue obtained at curettage. Therefore, such an artificial division of the end results of treatment serves only to befog the subject and to render impossible the application of the knowledge derived from end results.

To apply the authors' end results to the clinical patient, the figures in their Table VI for early and intermediate stages must be combined. This is done in Table A below.

TABLE A.

	EARLY PLUS INTERMEDIATE		
	TOTAL NO. OF CASES	NO. OF CASES SURVIVING FIVE YEARS	PER CENT FIVE-YEAR SURVIVAL
Hysterectomy	58	41 (28+13)	70.6
Hysterectomy plus x-ray, (with or without radium)	14	9 (5+4)	64.3
Hysterectomy plus radium, (with or without x-ray)	27	21 (19+2)	77.7

It is seen from this table that there is a significant difference in the end result in the group in which hysterectomy alone is employed from that in the group treated by radium plus hysterectomy, and that this difference favors the use of preoperative radium in certain groups of patients. It is probable, from the histologic specifications of the authors, that these groups correspond to the *clinical* Groups I and II as described by Healy and Brown (1939).

Although the figures in the authors' Table VI have been employed to illustrate the application of their end results to the clinical problem, there is a question as to the validity of the results arrived at in Table A. This is due to the fact that, in adding the number of cases in Table VI one obtains a total of 129, while the sum of the authors' subtotals in the last line of Table VI is only 121 and the total of determinate cases in their Table I is also 121. A recheck of the figures in Table VI would therefore seem essential.

A. J. FLAXMAN, M.D.

546 SURF STREET
CHICAGO 14, ILLINOIS
JANUARY 4, 1950

Reply by Dr. Speert

To the Editor:

Dr. Flaxman has raised three points, all of which can be clarified by reference to our paper. First, he questions the practicality, from the standpoint of therapy, of a classification of endometrial carcinoma based on pathologic examination of the excised uterus. Since we failed to demonstrate any benefit from preoperative radium, our initial procedure of choice is hysterectomy, regardless of the extent of uterine invasion. This factor, and the histologic grade of the tumor, may indicate the desirability of postoperative roentgen therapy, but it is scarcely necessary to make a decision on this point before hysterectomy is performed. Tumor classification based on pathologic examination is more significant than one based on clinical estimation of uterine size, since the latter is so often affected by coincident myomas.

Second, Dr. Flaxman has regrouped our data into his Table A, which he believes shows a "significant difference" in favor of preoperative radium. The difference is 7.1 per cent in terms of cases with five-year survival. Simple statistical treatment of the data in Dr. Flaxman's table will show that there is about a 50 per cent probability of a difference as large as or larger than this occurring by chance alone.

Third, the suggested recheck of the figures in our Table VI has shown them to be correct. Dr. Flaxman's arithmetical confusion apparently stems from his failure to note the following statement in our paper: "Since a few patients had both forms of irradiation, there is some overlapping between the second and third categories."

HAROLD SPEERT, M.D.

COLUMBIA-PRESBYTERIAN MEDICAL CENTER
NEW YORK, NEW YORK
JANUARY 11, 1950

Necrology

ARTHUR HENRY MORSE, B.A., A.M., M.D., obstetrician, and for thirty-five years a member of the Yale faculty, died of a cerebral hemorrhage on January 25, at his home near New Haven, Conn. Born in Salem, Mass., Dec. 13, 1880, a graduate of Tufts in 1902, and Johns Hopkins Medical School in 1906, where he served in the hospital as resident obstetrician, Dr. Morse became an instructor in obstetrics and gynecology at the University of California, and Associate Gynecologist at the University Hospital in San Francisco. In 1915 he joined the faculty of the Yale School of Medicine, becoming chief of the department in 1921, from which he retired in 1948. Dr. Morse was a Fellow of the American College of Surgeons, a member of the American Gynecological and many other specialist societies.

Items

Fellowship in Gynecologic Endocrinology

A fellowship in gynecologic endocrinology will be available in the Department of Obstetrics and Gynecology, Jefferson Medical College and Hospital, on July 1, 1950.

Applicants for the fellowship must have had at least a one-year residency or equivalent training in obstetrics and gynecology. Extensive clinical and laboratory facilities are available to the fellow, who will work under the supervision of Dr. A. E. Rakoff, Clinical Professor of Obstetric and Gynecologic Endocrinology, and members of the Endocrine Division of the department. Stipend $1,800 per year. For further details write to Lewis C. Scheffey, M.D., Professor of Obstetrics and Gynecology, Jefferson Medical College and Hospital, Philadelphia, Pa.

American Board of Obstetrics and Gynecology

The general oral and pathology examinations (Part II) for all candidates will be conducted at The Shelburne, Atlantic City, New Jersey, by the entire Board from Sunday, May 21, through Saturday, May 28, 1950. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates.

Candidates for re-examination in Part II must make written application to the Secretary's office not later than April 1, 1950.

Applications are now being received for the 1951 examinations. Application forms and Bulletins are sent upon request made to

PAUL TITUS, M.D., *Secretary*,
1015 Highland Building,
Pittsburgh 6, Pa.